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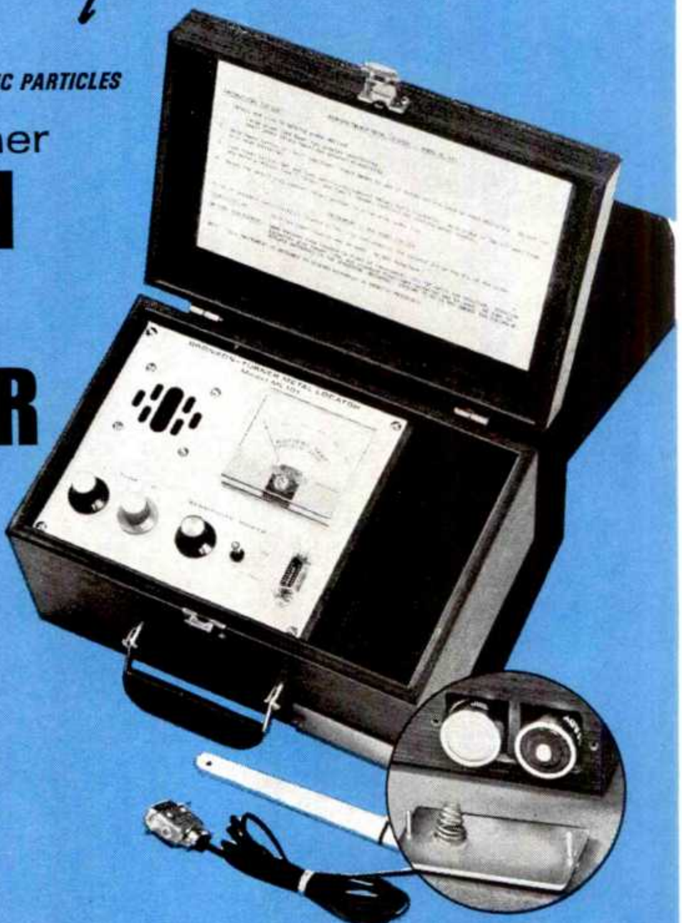

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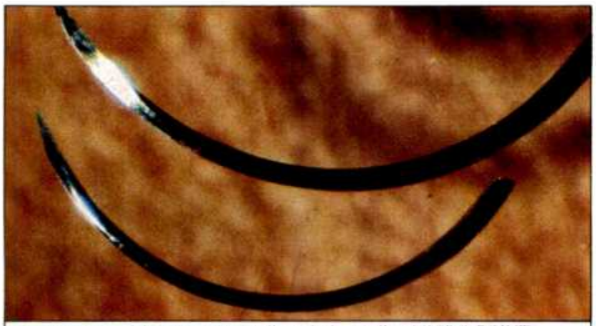

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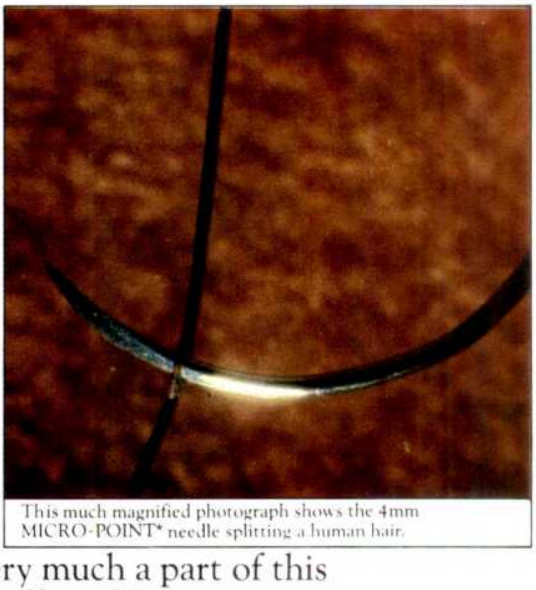

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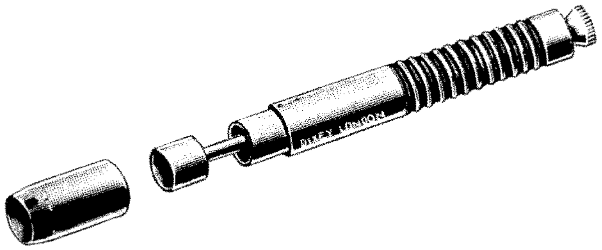

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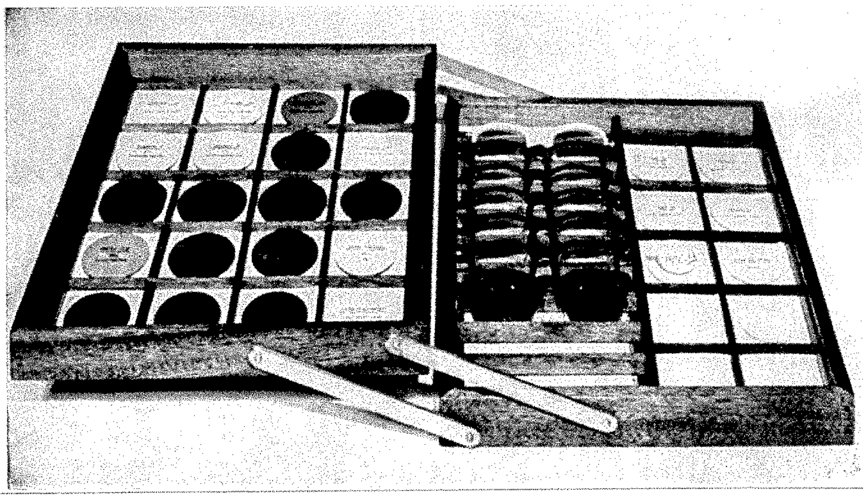

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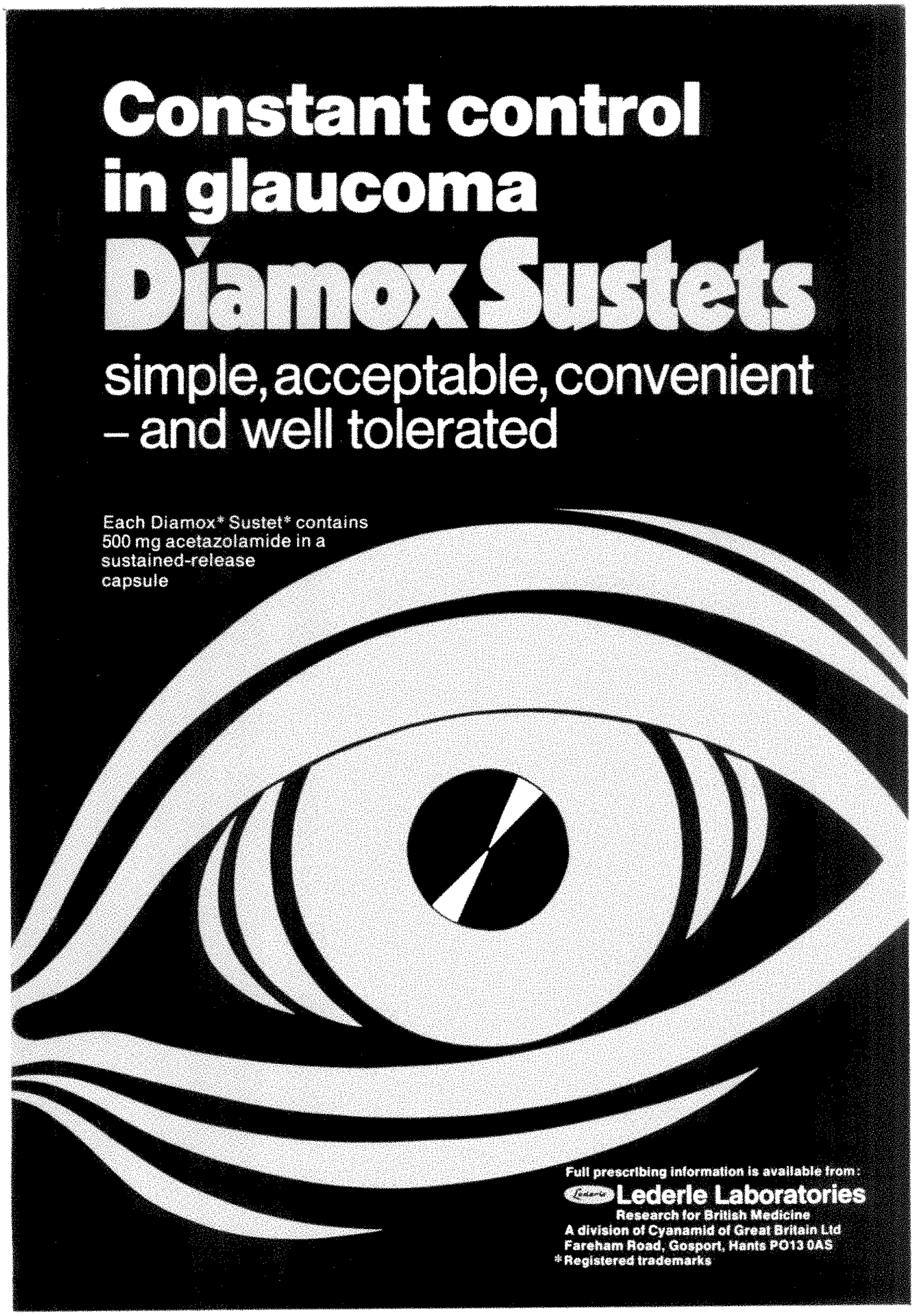

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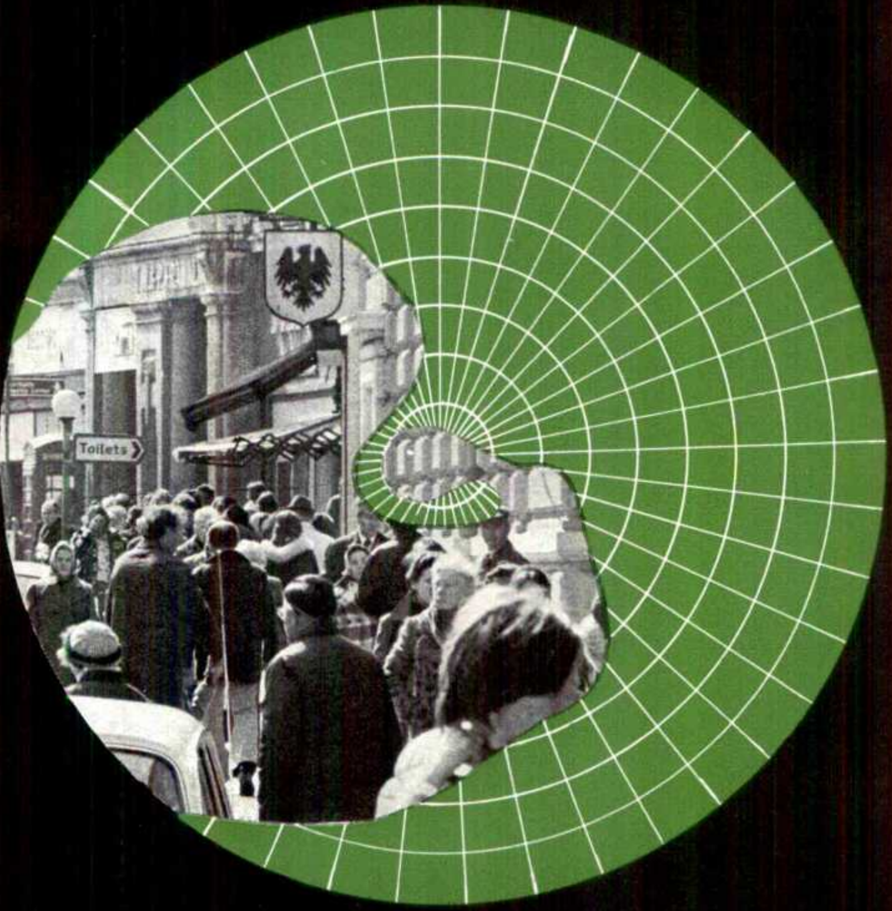

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Editorial: Management of non-paralytic strabismus in infants, with special reference to esotropia

In the treatment of any defect of physiological function in the human body the aim should be to restore or develop, and maintain, a normal state of affairs as soon as possible or, failing this, to improve that function to the greatest possible extent. In strabismus there may be three defects of function which need correction:

(1) A defect of normal visual function of the squinting eye and in some cases of the non-squinting eye also; (2) a defect or loss of normal binocular function; (3) a physical deformity caused by the deviation of the visual axes, which in some cases may be quite minimal.

With regard to the first, no real problem is likely to exist if the squint is freely alternating or if it occurs only intermittently. But if the squint is unilateral and constant, especially if the deviation is longstanding and was manifest in earliest infancy, the loss of visual acuity in the squinting eye may be considerable and may be associated with non-central fixation—an acquired and adaptive reaction and one which in general does not develop until a constant squint has been present for some time. So far as the second is concerned, this may develop as a result of a squint or in some cases it is possible that there is an underlying congenital defect of binocularity of heredofamilial origin. The third defect is the one that usually attracts the attention of parents, grandparents, or other observers, and its existence may be of the most profound importance because the physical deformity, if marked, may cause the parents and later the patient considerable social embarrassment. Indeed the squint itself and/or the defective visual acuity of a squinting eye may be a handicap in achieving certain forms of livelihood. It must, however, be appreciated that so far as visual acuity and binocular function are concerned a convergent squint of slight degree and not cosmetically obvious may be as pernicious in its effect on visual function as one of large degree.

In contradistinction it is interesting to note that normal or potentially normal binocular function is the rule rather than the exception in cases of primary *divergent* strabismus. This is probably because the deviation, at least in the early stages, is intermittent in nature or may occur only when viewing distant objects, being well controlled for near objects thanks to the power of convergence; or, less commonly, if there is an underlying convergence insufficiency, it may occur when viewing near objects only. Moreover, in exotropia any tangible degree of amblyopia is rare, since a diverging eye is invariably used for fixation when the patient is looking to the side of the deviation. Patients with a congenital divergent squint rarely get any worse if left untreated and invariably maintain their binocular potential. Hence the results of adequate surgical treatment, even if delayed until adult life, are usually most satisfactory. At any rate exotropia in children does not account for more than 15% of all cases of squint (R. M. Ingram, p. 4).

In cases of congenital ocular palsy of slight degree, including certain cases of the A and V syndrome and of Duane's retraction syndrome, it is amazing how normal binocular function is achieved and preserved by the adoption of a compensatory head posture and in the presence of a well-developed fusional reserve. These observations underline the innate desire for binocularity which appears to exist in most healthy infants. However, in squints of the convergent type with a fairly large deviation there is usually no position of the binocular gaze in which the infant can achieve binocular fixation. Hence the necessity for early and adequate treatment.

Although it is universally agreed that no child suffering from non-paralytic esotropia can be pronounced *cured* unless the visual acuity of each eye (with spectacle correction if needed) is of normal standard, and unless the ocular deviation has disappeared and the binocular function has become normal, yet in certain cases this ideal goal cannot be achieved, usually because the diagnosis of the condition has been made too late or the significance of the condition and the necessity for early treatment have not been fully realised.

Since esotropia of small angle may escape the notice of the average family doctor and yet may be associated with severe amblyopia in one eye, and since amblyopia due to anisometropia may exist in the presence of orthophoria, some form of screening of young children for visual defects caused by these conditions is most desirable.

As Ingram rightly points out, the treatment of amblyopia in a case of esotropia may have to await the recognition of the cosmetic deformity; and indeed only a little more than 50% of children with esotropia have a cosmetically noticeable deviation. He states that, although there is a first peak number of initial attendances of children with esotropia at the age of 3 or 4 years, there is also a second peak at the age of 5 years, when children first go to school and are subjected to a sight test. In his series he found that nearly 69% of cases of amblyopia presented after the age of 5 years and in three-quarters of these there was no detectable squint. Ingram therefore advocates an early screening test which is designed to identify both the squinter and the straight-eyed amblyope, for there is no doubt that the earlier a firm diagnosis of squint and/or amblyopia is made and the earlier the corrective treatment is applied the better the prognosis. The present system of vision testing on school entry (at 5 years of age) is obviously inadequate, and even if subjective testing of vision is made, as it can be in co-operative children of 2½ or 3 years of age, it may not give sufficiently accurate results to be of value. It also has the disadvantage of being very time-consuming.

Ingram therefore suggests that an examination of the refraction carried out under a cycloplegic should be used as a quick objective method of screening. The reason for this is based on the clinical research he has done, which shows: (1) +2·0 to +2·75 D of spherical hypermetropia in the more emmetropic of a pair of hypermetropic eyes is significantly associated with esotropia, and this is so even in the absence of anisometropia. It is also significantly associated with some degree of amblyopia irrespective of whether esotropia is present. This information is probably the first definite attempt to define what is an abnormal amount of hypermetropia in a child. (2) Anisometropia is significantly associated with esotropia, but only if cases of spherical hypermetropia of +2·0 D Sph or more in the more emmetropic eye are included. (3) In all cases of esotropia the added presence of anisometropia is significantly associated with an increased chance that the child will also become amblyopic. Ingram states that no improvement in the treatment of straight-eyed amblyopes nor of esotropia not cosmetically noticeable can be expected unless visual acuity can be adequately tested well before school entry, or some special screening test, e.g., refraction, is carried out. In routine screening procedures by objective refraction in 209 children of the preschool age (mainly between 1 and 2 years) who were found to have esotropia, 72% had an abnormal refraction. We await with interest the results of Ingram's treatment of his series of cases in terms of visual acuity and of binocular function.

There is no doubt that children who are 'at risk' with regard to squint and amblyopia should be subjected to early-eye examination including refraction. This refers to those families in which there is a history of 'squint', 'cast', 'turn', or 'lazy eye' in a child's mother, father, grandparents, siblings, aunts, uncles, or cousins or a history of any of these relations having had to wear glasses since early childhood. The paper by E. Chimonidou (p. 26), of Athens, supports the hereditary nature of strabismus which dates from early infancy. In the series of cases of squint seen in Greece 81·2% were convergent and 18·8% divergent, and in those suffering from amblyopia a satisfactory result (equal and normal vision in each eye) resulted in 60% of cases. These authors considered that a refractive error was significant when hypermetropia exceeded 3·0 D, when myopia of any degree was present, or when astigmatism was over 0·50 D or anisometropia over 1·0 D. No data are given as to binocular function.

The findings in the paper by Higham (p. 30) on stereopsis and aniseikonia in uniocular aphakia, although dealing with adults, should also apply to children. He finds that when aphakia is corrected with a contact lens it is in most patients no obstacle to binocular function. The comfort of the contact lens is, of course, an important factor. In the 27 uniocular aphakics he examined there were only 2 with no demonstrable stereopsis on the Titmus chart. The aniseikonia in these 2 patients was 25 and 29%, respectively; in all the other patients the aniseikonia was below 20%. In children with uniocular aphakia it would appear to be advisable to overcorrect the contact lens by +3 D and give the patient spectacles to neutralise this for distance.

The treatment of amblyopia first comprises full correction of the refraction. If this controls the deviation, and if it can be shown that normal retinal correspondence and fusion with a reasonable range is present, the constant wearing of glasses will in due course gradually lead to improvement of visual acuity of the amblyopic eye. The process can be hastened by part-time occlusion of the better-seeing eye. If, however, no binocular function can be demonstrated, constant occlusion of the better-seeing eye is indicated; and, once occlusion has achieved equal vision in each eye both for distance and near, regular occlusion of one or other eye should be practised until steps are taken to give the patient sufficient parallelism of the visual axes to enable him to obtain stimulation of the two foveae by images of the same object. This may be achieved by accurate surgical treatment, which may be needed in more than one stage or in the first instance by the use of prisms, aided, if indicated, by the use of orthoptic exercises.

Dr Pigassou in her paper (p. 16) with its inviting title of 'Entente cordiale in the early treatment of squint' questions the validity of Kenneth Wybar's statement (presumably with regard to the surgical treatment of esotropia in patients between the age of 5 and 6 years) that he regards as a highly satisfactory result a slightly anomalous type (of retinal correspondence), so that the condition represents a secondary form of microtropia. She believes that 'to cure a squinter is to give him normal binocular vision'. This may be so, but, if a small angle of deviation with anomalous fusion, a good range of fusion, and full stereopsis is achieved, the result is highly satisfactory to the patient and his parents and appears to give permanent stability. Prismotherapy as practised by Dr Pigassou is essentially preoperative and is accompanied by exercises to establish single binocular vision in artificial conditions followed by the development of fusion and then stereoscopic vision. If, initially, retinal correspondence is normal, exact prisms to correct the deviation are used. If, however, retinal correspondence is abnormal, overcorrecting prisms with an overcorrection of about 15 dioptres are used with change of the fixating eye.

In discussing the aim of early treatment Dr Pigassou points out that binocular vision is a conditioned reflex which develops in the first years of life, and if some factor causes an ocular deviation this will produce abnormal adaptations which must be destroyed before they become deep-rooted. She emphasises the importance of specially adapted orthoptic examination and treatment to suit the intellectual and sensory-motor capacities of the child, and the need for the full collaboration of the parents. She reports that the results of prismotherapy are amazingly good—100% of cures in children correctly treated. (Presumably those whose parents lacked the necessary co-operation to see that the treatment was correctly carried out were not included in the results.) She concludes that: (1) Thanks to early treatment, we should encounter in the future neither eccentric fixation nor anomalous retinal correspondence. (2) The functional treatment of strabismus should be begun between 1 and 3 years of age (this opinion is in line with current therapy of all developmental troubles). (3) Early treatment is possible only if the early detection of squint is organised and if appropriate techniques are used.

Similar statements were made by Dr E. Thomas 52 years ago in his opening paper at the Oxford Ophthalmological Congress of 1924. He said with regard to the treatment of convergent concomitant strabismus, 'Once we have the parents made to understand the importance of instant . . . attention to squint at whatever age it occurs we shall be in a fair way, I hope and think, to reduce the incidence of squint and amblyopia and shall have moved a step forward towards the ideal of prevention. . . . And when I have suggested a still higher ideal of prevention by the, preferably expert, examination of children before entering school I have done what I set out to do.'

British Journal of Ophthalmology, 1977, **61**, 4–7

The problem of screening children for visual defects

R. M. INGRAM
From the Kettering and District General Hospital

SUMMARY All the cases of squint and amblyopia referred to both hospital and school clinics in one district during one calendar year have been reviewed in order to clarify when, where, and how these cases first present to the ophthalmologist. The types of case at present seen in 'hospital' and 'school' clinics are quite different, and effective screening methods are unlikely to be developed if these two services continue to be regarded as separate entities. Exotropia is much less frequent than esotropia (only 15% of all cases of squint). The concept of a single peak number of first attendances of children with esotropia at age 3 to 4 years is not substantiated. There is a second peak at age 5 years, when children first go to school. In fact 49% first attended after their fifth birthday. The majority (69%) of cases of amblyopia presented after the age of 5 years. Three-quarters of these (46% of the total) have no clinically detectable squint. Neither they, nor those children who have a strabismic amblyopia, but not a cosmetically noticeable squint, will at present be detected until they have a sight test at school. This is a measure of the need to re-examine our long-established methods of screening children for amblyopia. One screening test designed to identify both the 'squinter' and the 'straight-eyed amblyope' is required.

Articles directly or indirectly criticising the 'late' discovery of children with squint and amblyopia appear regularly in the ophthalmic literature (e.g., Aaberg, 1968; Allen, 1967; Bettman and Fellows, 1961; Henderson, 1969; McNeil, 1955) and in other periodicals (e.g., McNeil, 1959; Miller, 1958; Nixseamann, 1970; Perkins, 1973). There is also the problem of non-strabismic amblyopia (e.g., Jampolski *et al.*, 1955; Jackson, 1964; Phillips, 1959; Robinson, 1961; Sugar, 1944). Such cases usually escape detection until their visual acuity is tested, because there is no cosmetically obvious squint. Recently attention has turned towards the possibility of selecting children particularly at risk for squint, in the neonatal period (Seba, 1972) and later (Karpowicz, 1965; Kramar, 1973; Pratt-Johnson and Lunn, 1967).

Programmes to screen children for visual problems should be directed towards detecting just those cases that might be expected to respond to treatment at an age when this is still possible. Innovations should logically be based on a pattern of referrals and the results of treatment of those identified by methods currently in use. Adelstein and Scully (1967) reported the age at which children with squint were referred, but so far as I know there had been no comprehensive review to include also those cases found to have amblyopia, in the absence of a squint detectable by the cover test, and defective vision associated with refractive errors (e.g., astigmatism and myopia) not usually associated with squint or amblyopia. Fusion of the school eye service with the hospital service in this area (Ingram, 1973) provided the administrative and records facilities suitable for this study, which was designed to define the age of referral and mode of detection for the whole range of visual problems in one district during the period of one calendar year. Attention is drawn particularly to convergent squint and amblyopia.

Sample of children

Every child seen in the children's eye clinics at Kettering General Hospital and the Nuffield Diagnostic Centre at Corby during the period 1 November 1971 to 31 October 1972 was included. Ninety-one children were referred for what may be termed 'non-visual' problems. They have been excluded from the main part of the report, but they were investigated in the same manner as those with 'visual' problems because they might be representative of the population as a whole in some respects.

The main sample of the report comprises 665 children. All were referred by general practitioners, or as a result of a sight test at school with a provisional diagnosis of strabismus and/or visual defect. Collection of the sample continued for the period of one calendar year because Adelstein and Scully

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(1967) reported a seasonal incidence in the onset of squint and its referral.

Theoretically all cases of strabismus and/or amblyopia pass through an ophthalmologist's care at some stage. In this area they would pass through one of the two children's eye clinics mentioned above. Communications here are good between the children's eye clinic on the one hand and the general practitioners, opticians, and public health authorities on the other, and there are reasonable grounds for believing that nearly all the cases of strabismus or amblyopia detected during the year have been included in this survey. The drawing area of the 'general practitioner' and 'school' referrals can only be estimated and may not be quite the same. There is probably a slight excess of 'general practitioner' referrals (180 000 population) over 'school' referrals (140 000 population). There might also be a slight deficiency of the 10+ age group of children who have myopia, because some of these may have been seen by opticians without referral to hospital or school clinic. Apart from these two factors the sample presented here is probably representative of a general pattern of children found to have eye defects.

All the cases were 'new' in the sense that none of them had had any ophthalmic treatment or investigation anywhere before they were seen in this clinic.

Methods

The following information was recorded for each child:

(1) Source of referral.

(2) Age when first seen.

(3) Presence of strabismus detectable by the cover test. Children with an esophoria which breaks down on cover test to be an intermittent esotropia were recorded together with children who have a constant esotropia as 'esotropia'. It is accepted that microstrabismus is not detected by the cover test, which 'misses' deviations of less than two prism dioptres (Romano and von Noorden, 1971) and microtropia with identity.

(4) If manifest strabismus was diagnosed, the duration of the deviation was noted.

(5) Refraction (see Ingram, 1977).

(6) Presence of amblyopia. All visual acuities were measured on either a full Snellen chart or by using the linear Sheridan-Gardiner test. This eliminates the inaccuracies in vision testing if single letter charts are used (Hilton and Stanley 1972; von Noorden, 1970).

Visual acuity could not be recorded in a number of children, e.g., very nearly all those under the age of 3 years. A total of 59 cases have therefore been recorded as ?amblyopia. Twenty-six of these were children under the age of 4 years who had esotropia which was not spontaneously alternating and in whom there were good grounds for believing that the deviating eye was amblyopic. It was not possible to obtain a visual acuity on the first attendance of the remaining 39 older children, and none of those kept a follow-up appointment to be seen after they had received their glasses (nine of these had a uniocular esotropia and 21 had a refractive error which we now know to be significantly associated with amblyopia, e.g., hypermetropia or anisometropia, and three other children had astigmatism).

(7) The family history was recorded as positive if there was a history of squint, 'cast', 'turn', or 'lazy eye' in mother, father, siblings, aunts, uncles, or cousins. A history of either parent or a sibling wearing glasses constantly was also recorded.

Findings

Table 1 *Source of referral and diagnosis*

	G.P. referrals	*School referrals*
N.A.D.	88	141
Myopia	1	144
Squint	96	64
Hypermetropic anisometropia	8	76
Hypermetropic astigmatism	0	13
Hypermetropia	9	10
No refractive error or squint, but amblyopia	0	15
	202	463

Table 2 *Pattern of referral of children with esotropia*

Age	*G.P./Hospital*	*School*
0	7	—
1	11	1
2	12	3
3	23	1
4	11	—
5	9	15
6	4	12
7	3	6
8 –	4	15
	84	53

Table 3 *Pattern of referral of cases of amblyopia or probable amblyopia*

Age	*GP/Hospital*	*School*
0	10	—
1	11	—
2	14	2
3	16	—
4	8	1
5	4	37
6	4	26
7	2	13
8 –	4	44
	73	123

Discussion

The majority of children presenting with 'visual' problems were identified by the school or public health authorities suspecting some defect, the ratio of patients, school clinic to hospital clinic, being 2·29 : 1 (Table 1). Strabismus was seen predominantly in the hospital clinic in a ratio of 1·5:1 (Table 2), but cases of amblyopia or ?amblyopia attended predominantly the school clinic in a ratio of 1·68 : 1 (Table 3). On the basis of these figures alone it seems illogical to have two separate services to treat strabismus and amblyopia. It does not really matter which clinic the children first attended; what is important is the age at which they presented.

There are two peak ages when children with esotropia presented, namely, 3 to 4 years and 5 to 6 years (Fig. 1). This is different from the picture presented by Adelstein and Scully (1967). The pattern for 'hospital' (i.e., general practitioner) referrals is very similar to the commonly held image, as presented in the 'hospital' cases of Adelstein and Scully's group (1967), but it is important to realise that 49% of the total were identified after the age of 5, and these children do not usually attend a hospital clinic.

In this area general practitioners' cases are usually seen within two weeks of the possibility of squint being mentioned by the parents, and I feel that these 49% do not represent neglect on their part. Few have cosmetically noticeable deviations, and those that do seem to occur in 'problem' families. The majority, however, are small-angled deviations, not cosmetically noticeable, and they are diagnosed only when an ophthalmologist does a cover test. By contrast most of the preschool age cases of esotropia have a cosmetic defect which is readily noticeable.

The pattern of referral of amblyopia is demonstrated in Table 3 and Fig. 2, but the cardinal point is that 69% of amblyopic children were not identified until after they had gone to school. While 78% of the amblyopic children who presented before the age of 5 years had a clinically detectable esotropia, 75% of those presenting with amblyopia after the age of 5 years had no such clinically detectable squint. These latter represent 46% of the total number of children found to have amblyopia.

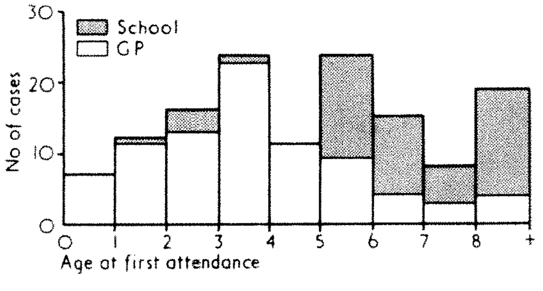

Fig. 1 *Referral of cases of esotropia.*

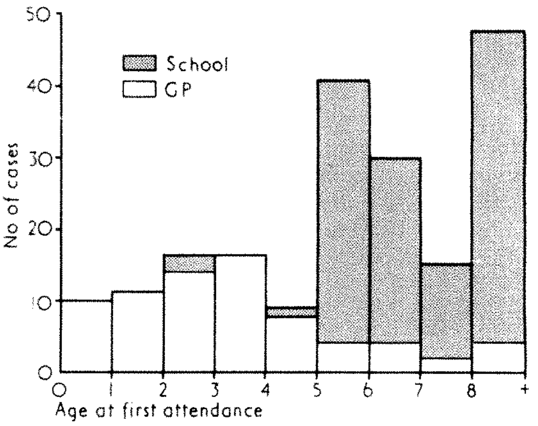

Fig. 2 *Referral of amblyopia or ? amblyopia.*

It is predictable that the majority of cases of myopia will be seen in the school clinic; but 90% of the 'straight-eyed' anisometropes also presented this way. In respect of these two types of case the hospital and school clinics are quite different. Children with exotropia formed only 15% of the total number of cases of squint (24 out of 160), and as they presented a variable clinical pattern they have been excluded from further discussion.

Screening: the problem

Treatment of amblyopia associated with a manifest squint has to await the recognition of the cosmetic deformity of squint, but little more than 50% of children with esotropia have a cosmetically noticeable defect. On the other hand no improvement can be expected with either the 'straight-eyed' amblyopes or the child with a squint which is not cosmetically noticeable under the present system, unless either they have their visual acuity checked earlier than school entry or some totally different screening test is devised for use at an earlier age.

The current argument in favour of screening before school entry has been set out by Simons and Reinecke (1974). It implies subjective testing on 3 and 4-year-old children as has been advocated by Aaberg (1968), Allen (1957), Cashell (1969), Cholst *et al.* (1962), Costenbader and O'Neill (1968), Giles (1970), Jackson (1964), Perkins (1973), Press and Austin (1968), Rosenthal and von Noorden (1971), and possibly others. This method of screening has actually been tried by Amigo (1973), Cunningham (1959), Hufhines (1961), Hyams and Neumann

(1972), Kohler and Stigmar (1973), Kaivonen and Kostenaja (1963), Nordlow and Joachimsson (1962), and Oliver and Nawratzki (1971), but it has never become established as a screening programme. Why? Possibly this is because any objective method, whether it be for visual acuity or anything else (e.g., stereopsis—Reinecke and Simons, 1974; Walraven, 1975), has the following disadvantages:

(*a*) It is time-consuming (and therefore expensive), and a number of children just do not respond—'untestability' (Lippmann, 1969).

(*b*) If the standard required for passing is harsh, then you get an excess of false positives, and if the standard required is low you 'miss' a number of defects (Kohler, 1973).

(*c*) A variable/low attendance for examination (Sutcliffe, 1960).

No method is likely to be perfect, but the first of these disadvantages could be overcome by employing a quick objective method of screening. Most of the 'straight-eyed amblyopes' have anisometropic refractive errors, and this must make one think seriously of refraction as an alternative to subjective testing in preschool children. It could be carried out before the age of 3 years, and if Kramar (1973) is correct with regard to the possibility of predicting strabismus, there is a possibility that we may screen, in one test, not only for non-strabismic amblyopia but also for strabismus and strabismic amblyopia as well. The only alternative is to use the family history as a guide to selecting children 'at risk'.

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Refraction as a basis for screening children for squint and amblyopia

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SUMMARY +2·00 to +2·75 dioptres of spherical hypermetropia in the more emmetropic of a pair of eyes is significantly associated with esotropia ($P < 0·001$) and the presence of amblyopia ($P < 0·01$). Anisometropia is not significantly associated with esotropia ($P = 0·31$) unless there is spherical hypermetropia of +2·00 dioptres or more in the more emmetropic eye ($P < 0·001$). Hypermetropic anisometropia of +1·00 DS or +1·00 D.Cyl. is associated with the presence of amblyopia ($P < 0·001$). In the absence of esotropia there is also a significant association between the amount of anisometropia and the initial depth of amblyopia ($P < 0·01$). The additional presence of esotropia increases the depth of amblyopia further ($P < 0·05$) but not the incidence of amblyopia ($P > 0·30$). The level of significance of the association of refractive errors with squint/amblyopia was itself significantly higher ($P < 0·01$) than that between a family history of squint or 'lazy eye' on the one hand and squint and/or amblyopia on the other hand. 72 ± 3% of all cases of esotropia and/or amblyopia in this sample of children had a refractive error of +2·00 DS or more spherical hypermetropia in the more emmetropic eye, or +1·00 D. or more spherical or cylindrical anisometropia. Since there is a close association between the refraction and how, when, and whether a child presents with squint and/or amblyopia, it would seem reasonable to reconsider refraction as a basis for screening young children for visual defects.

The problems of our present subjective methods of identifying squint, and particularly amblyopia, have been outlined (Ingram, 1977), and it was suggested that an objective method of screening might be better. Kramar (1973) has even suggested that the detection of certain refractive errors might be used to predict the appearance of squint. A study of the literature showed how little has been established about the association of refractive errors with strabismus/amblyopia and the finding that +2·00 to +2·75 dioptres of spherical hypermetropia in the more emmetropic of a pair of eyes was significantly ($P < 0·01$) associated with esotropia in children seen before the age of two years (Ingram, 1973) was surprising.

The purpose of this paper, therefore, is to report the refractions of the sample of children just described (Ingram, 1977). Abnormal amounts of hypermetropia and anisometropia in children are defined and the possibility of refraction as a basis for earlier detection of squint and amblyopia is compared with the use of a family history of these conditions.

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Methods

Many of the myopes were refracted without cycloplegia, but *all* other cases, irrespective of whether they had any defect of visual acuity or possibility of strabismus, and *all* those referred with 'non-visual' problems were refracted after full cylcoplegia with either 1% Atropine or 1% Cyclogyl. The refraction of each eye was obtained after retinoscopy at a working distance of one metre and subtraction of +1·75 dioptres, in each meridian, and recorded in plus spheres and plus cylinders. All refractions have been carried out by the author.

Method used to record the refraction

Pendse (1954) has drawn attention to the absence of an internationally acceptable method of recording refraction. The method that has been used most commonly is to record the spherical equivalent or the mean of the spherical equivalents of the two eyes. This method, which has been criticised by

Johnstone and McLaren (1963), is satisfactory for recording broad overall changes in the refraction of large population samples, but it does not allow for enough of the details which are so necessary for this type of investigation.

Therefore the amount of hypermetropia (or myopia) is presented as the spherical refraction of the more emmetropic meridian of the more emmetropic eye. Astigmatism was recorded separately, but up to +1·5 dioptres of astigmatism in the more emmetropic eye has been ignored, and it is accepted that this is open to criticism.

Several methods of recording anisometropia have previously been used. Jampolski *et al.* (1955) has specifically criticised the use of spherical equivalents. Stevens (1960) distinguished between spherical and astigmatic anisometropia, but used in his summary 'the difference between the meridia with the maximum refractive errors in each eye for deciding the degree of anisometropia', a method also used by Nordlow (1970). The difference between spherical and cylindrical anisometropia has been ignored in other reports (e.g., Killen, 1961, and Jackson, 1964), but it seemed right to record the two types separately, if only because there was a need to clarify what level of each is significantly associated with squint or amblyopia. Horwich (1964) for example queried whether cylindrical anisometropia is really associated with amblyopia. In this study, either +1·00 D. Cyl. or +1·00 D. Sphere difference between the appropriate meridia of the two eyes has been arbitrarily selected as warranting separate recording as anisometropia.

The depth of amblyopia (where possible)

Visual acuity was measured on a Snellen chart or by means of a linear Sheridan-Gardiner test. The corrected visual acuity has not been recorded, because many 3 to 6-year-old children will admit to only 6/9 or 6/12 acuity with a perfectly normal eye. However, the difference between the corrected acuity of the two eyes in one individual can fairly be regarded as the depth of amblyopia. Thus, a child having corrected acuities of 6/6 and 6/6 partly is recorded as having < 1 line of amblyopia. A child who has a corrected visual acuity of 6/6 and 6/9 or 6/9 partly has been recorded as having < 2 lines of amblyopia, as would a child who had acuities of 6/12 and 6/18 or 6/18 partly.

All this information was stored in, and subsequently retrieved from, a punch-card system used on the Delcopex machine.

Findings

All the circumstances when there might be an association between refraction or a family history on the one hand and esotropia and/or amblyopia on the other hand have been analysed. The numbers of children involved and the statistical analysis for each set of circumstances are given and the clinical significance is discussed later. Children presenting for 'non-visual' problems are compared with others in a few instances because in some respects they may be thought to represent the child population at large.

Table 1 *Hypermetropia, esotropia, and amblyopia*

A. Hypermetropia (all cases) and esotropia

	No squint	*Eso.+*	*Total*
0 to +1·75 DS	314	59	373
+2·00 to +2·75 DS	18	30	48
	332	89	421

$\chi^2 = 52{\cdot}8$ D.F. = 1 $P<0{\cdot}001$

B. Hypermetropia and esotropia, children with anisometropia excluded

	No Eso.	*Eso.+*	*Total*
0 to 1·75 DS	254	41	295
+2·00 to +2·75 DS	11	22	33
	265	63	328

$\chi^2 = 49{\cdot}9$ D.F. = 1 $P<0{\cdot}001$

Table 2 *Hypermetropia and amblyopia (including children with anisometropia)*

	No Amb.	*Amblyopia*	*Total*
0 to +1·75 DS	226	87	313
+2·00 to +2·75 DS	15	18	33
	241	105	345

$\chi^2 = 8{\cdot}88$ D.F. = 1 $0{\cdot}01>P>0{\cdot}001$

Table 3 *Anisometropia and esotropia*

A. Anisometropia (all cases) and esotropia

	No squint	*Eso.+*	*Total*
No anisometropia	421	88	509
Anisometropia+	84	49	133
	505	137	642

$\chi^2 = 22{\cdot}87$ D.F. = 1 $P<0{\cdot}001$

B. Anisometropia and esotropia
(excluding children with +2·00 or more D. Spherical hypermetropia in the more emmetropic eye)

	No squint	*Eso.+*	*Total*
No anisometropia	421	88	509
Anisometropia, but no hypermetropia in 'better eye'	65	19	84
	486	107	593

$\chi^2 = 1{\cdot}05$ D.F. = 1 $P = 0{\cdot}31$

(Table 3 continued on next page)

Table 3 *(continued)*

C. Anisometropia + hypermetropia and esotropia

	No squint	*Eso. +*	*Total*
0 to +1·75 DS	65	19	84
+2·00 DS or more in 'better' eye	19	30	49
	84	49	133

χ^2 = 18·20 D.F. = 1 P<0·001

	No squint	*Eso. +*	*Total*
0 to +1·75 DS	65	19	84
+2·00 DS to +2·75 DS in 'better' eye	7	8	15
	72	27	99

Exact probability 0·02

Table 4 *Anisometropia and presence of amblyopia*

A. Anisometropia and presence of amblyopia (in children presenting with esotropia)

	No Amb.	*Amb. +*	*Total*
No anisometropia	34	36	70
Anisometropia +	4	28	32
	38	64	102

χ^2 = 10·73 D.F. = 1 0·01>P>0·001

B. Anisometropia, esotropia, and presence of amblyopia

	No Amb.	*Amb. +*	*Total*
Esotropia	4	28	32
No esotropia	17	57	74
	21	85	106

χ^2 = 0·95 D.F. = 1 0·50>P>0·30

C. Spherical anisometropia and presence of amblyopia (children with esotropia excluded; figures taken from Table 7)

	No Amb.	*Amb. +*	*Total*
No anisometropia	190	19	209
+1·00 to +1·75 DS anisometropia	4	16	20
	194	35	229

χ^2 = 65·5 P<0·001

D. Cylindrical anisometropia and presence of amblyopia (children with esotropia excluded)

The association of +1·00 to +1·75 D. Cyl. anisometropia (but no spherical anisometropia) with amblyopia seems apparent, although the number of cases with this limited amount of anisometropia is not sufficient for statistical analysis:

Amblyopia	0	<1	<2	<3	<4	<5	5+
Anisometropia							
No aniso.	190	11	4	1	1	1	1
+1·00 to +1·75 D. Cyl.	7	5	2	2	1	0	0

However, there is a statistically significant association between cylindrical anisometropia of +1·00 D. or more (but no spherical anisometropia) and amblyopia (figures taken from Table 7):

	No Amb.	*Amb.*	*Total*
No aniso.	190	19	209
+1·00 D. Cyl. or more	10	13	23
	200	32	232

χ^2 = 35·3 P<0·001

The initial visual acuity and, therefore, the depth of amblyopia was not known in 27 out of 133 children who presented with anisometropic refractive errors.

There is a quantitative relationship between the amount of anisometropia and the initial depth of amblyopia when the remaining children are considered, e.g.:

Table 5 *Anisometropia and depth of amblyopia*

A. Amblyopia	0 to <2 lines	<3 lines or more	*Total*
Anisometropia			
0 to +1·75 DS ± Cyl.	48	27	75
+2·00 or more DS ± Cyl.	7	24	31
	55	51	106

χ^2 = 13·47 D.F. = 1 P<0·001

This association is still significant when a more limited range of anisometropia is compared at different depths of amblyopia, thus:

B.	0 to <1 line	<2 lines or more	*Total*
+1·00 to +1·75 DS ± Cyl.	17	24	41
+2·00 or more DS ± Cyl.	3	28	31
	20	52	72

χ^2 = 7·38 D.F. = 1 P<0·01

	0 to <2 lines	<3 lines or more	*Total*
+1·00 DS to +1·75 DS ± Cyl.	26	15	41
+2·00 DS or more ± Cyl.	7	24	31
	33	39	72

χ^2 = 10·27 D.F. = 1 P<0·01

	0 to <3 lines	<4 lines or more	*Total*
+1·00 to +1·75 DS ± Cyl.	36	5	41
+2·00 or more DS ± Cyl.	13	18	31
	49	23	72

χ^2 = 15·04 D.F. = 1 P<0·001

Table 6 *Anisometropia, esotropia, and depth of amblyopia*

A. Anisometropia ± esotropia and depth of amblyopia (all cases)

	0 to <2 lines	<2 lines or more	*Total*
No esotropia	44	30	74
Esotropia	11	21	32
	55	51	106

χ^2 = 4·67 D.F. = 1 P<0·05

This also applies where the amount of anisometropia is restricted to, say, a range of +1·00 to +1·75 D. Sphere, ± cylindrical anisometropia:

B.	0 to <2 lines	<2 lines or more	*Total*
No esotropia	36	12	48
Esotropia	11	15	26
	47	27	74

χ^2 = 6·43 D.F. = 1 P<0·01

Table 7 *Anisometropia (excluding esotropia) and depth of amblyopia*

Amblyopia Anisometropia	Sph.	Cyl.	0	<1	<2	<3	<4	<5	5+
	0	0	190	11	4	1	1	1	1
	0	+1·00 or more	10	6	3	3	1	—	—
	+1·00 to +1·75	0	4	4	5	5	1	1	—
	+1·00 to +1·00 to +1·75	+1·00 or more	2	2	1	1	—	—	—
	+2·00 to +2·75	0	1	1	3	2	1	—	—
	+2·00 to +2·75	+1·00 or more	—	—	1	1	1	—	—
	+3·00 or more	0	—	—	—	1	3	1	3
	+3·00 or more	+1·00 or more	—	—	—	1	1	—	3

	0 to <1 line	<2 lines or more	*Total*
+1·00 to +1·75 DS ± Cyl.	12	14	26
+2·00 DS ± Cyl.	2	22	24
	14	36	50

χ^2 = 7·08 D.F. = 1 P<0·01

	0 to <2 lines	<3 lines or more	*Total*
+1·00 to +1·75 DS ± Cyl.	18	8	26
+2·00 DS ± Cyl.	6	18	24
	24	26	50

χ^2 = 8·09 D.F. = 1 P<0·01

	0 to <3 lines	<4 lines or more	*Total*
+1·00 to +1·75 DS ± Cyl.	24	2	26
+2·00 DS ± Cyl.	11	13	24
	35	15	50

χ^2 = 10·7 D.F. = 1 P<0·01

Table 8 *Hypermetropia and the age of presentation*

A. Esotropia: hypermetropia and age of presentation ± 5 years

	0–4 years	*5+ years*	*Total*
0 to +1·75 DS	22	37	59
±2·00 DS or more	48	30	78
	70	67	137

χ^2 = 6·96 D.F. = 1 P<0·01

B. Esotropia; hypermetropia and age of presentation ± 4 years

	0–3 years	*4+ years*	*Total*
0 to +1·75 DS	19	40	59
+2·00 DS or more	40	38	78
	59	78	137

χ^2 = 4·239 D.F. = 1 P<0·05

C. Anisometropia; hypermetropia and age of presentation ± 5 years

	0–4 years	*5+ years*	*Total*
0 to +1·75 DS	9	75	84
+2·00 DS or more	20	29	49
	29	104	133

χ^2 = 14·72 D.F. = 1 P<0·001

In respect of a family history of squint or 'lazy eye', children presenting with a 'non-visual' problem could be considered as representative of the child population. The incidence of a family history in these children (see Table 10C) is, therefore, compared with the family history of those presenting with visual problems:

Table 9A and B *Family history of squint or 'lazy eye'*

A. Children presenting with esotropia

	F.H.+	*F.H.–*	*Total*
Esotropia	79	58	137
Non-visual problem	32	59	91
	111	117	228

χ^2 = 10·20 D.F. = 1 0·01>P>0·001

B. Children presenting with esotropia and/or amblyopia

	F.H.+	*F.H.–*	*Total*
Esotropia and/or amblyopia	111	98	209
Non-visual problem	32	59	91
	143	157	300

χ^2 = 7·48 D.F. = 1 0·01>P>0·001

The incidence of a family history of squint or 'lazy eye' was not significantly different when myopes were compared with children presenting with a 'non-visual' problem (χ^2 = 0·21 P>0·50), although there was a significant difference when myopes were compared with those who had esotropia (χ^2 = 17·16 P<0·001).

Table 9C

C. Children presenting with hypermetropia, hypermetropic astigmatism or anisometropia

	F.H.+	*F.H.–*	*Total*
Hypermetropic refractive errors	104	108	212
Non-visual problem	32	59	91
	136	167	303

χ^2 = 4·42 D.F. = 1 0·05>P>0·02

A family history of parent or sibling wearing spectacles constantly (for any reason) was not significantly associated with children presenting with esotropia (χ^2 = 1·33 P>0·20) or hypermetropia, hypermetropic astigmatism, or anisometropia (χ^2 = 0·80 P>0·30), but it was significantly associated in the case of children presenting with myopia (χ^2 = 5·97 P<0·02).

Table 10 *Findings in children who presented with a 'non-visual' problem*

A. Presenting diagnosis

Epiphora/naso-lacrimal duct obstruction	31
Chalazion	18
Injuries	12
Keratitis/corneal ulcer (including corneal FBs)	9
Lid abnormalities (entropion, ptosis, blepharitis, trichiasis, papilloma)	8
Conjunctivitis	5
Dacryocystitis	2
'Sore eyes'—N.A.D.	2
Orbital cellulitis	1
Albinism	1
Dermoid cyst	1
Migraine	1
	91

B. Spherical refraction of the more emmetropic eye

0 to +1·75 D. = 76 (85%)
Of these,
- 2 had +1·75 to +2·50 D. astigmatism
- 5 had spherical anisometropia of +1·00 to +1·75 D.
- 1 had spherical anisometropia of >+3·00 D., and cylindrical anisometropia of +2·00 to +2·75 D.
- 2 had cylindrical anisometropia of +1·00 to +1·75 D.

+2·00 to +2·75 D. = 8.
+3·00 to +3·75 D. = 2. Of these,
- 1 had spherical anisometropia of +1·00 to +1·75 D.

+4·00 to +4·75 D = 0.
5·00 D. or more = 1.
Myopia = 4.
91

C. Family history

40 cases (44% of total) had no F.H. whatever of abnormalities.
35 cases (38% of total) had F.H. of parent or sibling wearing glasses.
32 cases (35% of total) had some F.H. of strabismus or amblyopia.
6 of the 9 cases of 'significant' anisometropia had a F.H. of parent or sibling wearing glasses or somebody with strabismus or amblyopia.
8 of the 11 cases with 'significant' hypermetropia had a similar F.H.

Discussion

HYPERMETROPIA, ESOTROPIA, AND AMBLYOPIA

+2·00 to +2·75 D. of spherical hypermetropia in the more emmetropic of a pair of eyes is significantly (Table 1A, $P<0{\cdot}001$) associated with esotropia, thus confirming earlier observations (Kramar, 1973; Ingram, 1973), and this is so even in the absence of anisometropia (Table 1B, $P<0{\cdot}001$). It is also significantly (Table 2, $P<0{\cdot}01$) associated with some degree of amblyopia, irrespective of whether esotropia is present. So far as I know, this is the first attempt to define what is an abnormal amount of hypermetropia in a child.

ANISOMETROPIA AND ESOTROPIA

Anisometropia is significantly (Table 3A, $P<0{\cdot}001$) associated with esotropia, but only if cases with spherical hypermetropia of +2·00 DS or more in the more emmetropic eye are included (see Tables 3B and 3C). This confirms the original findings of Phillips (1959) but not his more recent ones (Phillips, 1966).

ANISOMETROPIA AND AMBLYOPIA

Two questions require an answer. Firstly, what amount of anisometropia is associated with the presence of amblyopia? Different levels have been quoted in the literature for this, e.g., two dioptres, spherical or cylindrical not stated (Kamiya *et al.*, 1968; Kesby, 1967), 1·5 D. spherical or 1·0 D. spherical and a cylindrical anisometropia (Bishop, 1957), 1·0 D. spherical (Scobie, 1951). Costenbader *et al.* (1944) simply say that the higher the amount of anisometropia, so the higher is the incidence of amblyopia.

Secondly, what is the relation between the amount of anisometropia and the depth of amblyopia? Lagleyze originally stated that they were roughly proportional to each other. This view has been supported by Copps (1944) and Guzzinati (1957), but it has been questioned by Helveston (1966) and more recently Malik *et al.* (1968) have stated that the depth of amblyopia is related only to the degree of eccentricity of fixation, this being independent of the amount of anisometropia.

In this sample, taking all cases of esotropia, the added presence of anisometropia is significantly associated with an increased chance that the child will also be amblyopic (Table 4A, $P<0{\cdot}01$). Although the presence of esotropia in addition to anisometropia does not increase the chance of amblyopia being present (Table 4B, $P>0{\cdot}30$), it does nevertheless increase the depth of amblyopia when this is present (Table 6A, $P<0{\cdot}05$). If only the lower amounts of anisometropia (+1·00 to +1·75 D. sphere ± Cyl.) are considered, the difference is even more significant (Table 6B, $P<0{\cdot}01$). The additional presence of esotropia, therefore, complicates the association between the amount of anisometropia and the depth of amblyopia.

In this series, taking all those cases without the complicating factor of esotropia, it is clear that +1·00 to +1·75 D. Sphere (Table 4C, $P<0{\cdot}001$) or +1·00 D. or more cylindrical anisometropia (Table 4D, $P<0{\cdot}001$) is significantly associated with the presence of amblyopia.

Neither Copps (1944) nor Guzzinati (1957) differentiated between those with and those without a manifest strabismus. Helveston (1966), however, did but the number (20 without squint) in his series is not sufficient for statistical analysis. Malik *et al.* (1968) admit that among their cases with central fixation, 'there is a tendency for the visual acuity to be better in cases with a low degree of anisometropia'. Statistical analysis of the figures in Table 1 of their paper, comparing 0 – 3 D. with 3 +D. of anisometropia does show that significantly more of those with the lower level of anisometropia have a visual acuity of 6/18 or better. If a similar calculation is done on all their cases, i.e., those with and those without central fixation, the association is still significant, though less so. Their cases presumably included some with and some without a manifest squint. In this series the number of cases with anisometropia and esotropia is not sufficient for statistical analysis. However, the number of children with anisometropia without esotropia is sufficient for statistical analysis and there is clear evidence that a larger amount of anisometropia is associated with an increased depth of amblyopia (Table 7, $P < 0{\cdot}01$). No record was kept of the fixation of the anisometropic eye in these children, but the fact of the added presence of esotropia further increases the depth of amblyopia (Table 6) could indicate that the fixation pattern is also relevant in determining the depth of amblyopia.

ASTIGMATISM

No conclusions can be drawn on the clinical significance of hypermetropic astigmatism because there were only eighteen children with > +1·50 D. in the more emmetropic eye in this series. Only one of these eighteen had a squint (divergent); but five of them also had a significant amount of anisometropia, and four of these were known to be amblyopic.

REFRACTIVE ERRORS AND THE AGE OF PRESENTATION

In this sample, a child with esotropia and/or amblyopia, and found to have +2·00 or more DS in the more emmetropic eye, probably presented before the age of five years (Table 8A $P < 0{\cdot}01$). If he had less than +2·00 DS, he probably presented after the age of 5. A similar relationship holds good if one makes the dividing line for age arbitrarily at 4 years (Table 8B $P < 0{\cdot}05$), but not at 6 years ($P < 0{\cdot}3$).

Similar observations can be made in respect of those children who have anisometropia. If such a child presented before the age of 5 years, he was significantly more likely to have +2·00 or more DS of hypermetropia in the more emmetropic eye (Table 8C $P < 0{\cdot}001$). If he presented at or after the age of 5 the reverse is true.

These observations seem to offer a basis for predicting when (± five years) and how (with or without esotropia, with or without amblyopia) a child with a given refractive error should present under the present system.

IDENTIFYING CHILDREN 'AT RISK'

It is currently fashionable in paediatrics to identify very young children who are particularly at risk for specific conditions, and investigate or follow them up appropriately. Sheridan (1960) believed that it was impractical to apply vision screening tests to all infants, but nevertheless suggested that we should concentrate on children 'at risk'. Refraction might prove to be a method of identifying these children.

OBJECTIVE METHODS OF SCREENING

An objective screening test, such as refraction, has been tried before (Hirsch, 1950; Tyser and Letchworth, 1949). The advantages are that it is quick and it can theoretically be applied at any age. Also, at one single screening procedure, it might identify the different types of case currently presenting to the separate 'school' and 'hospital' clinics, i.e., those whose problem will not otherwise be identified until their visual acuity is checked and those whose cosmetic deformity draws attention to there being an abnormality. In this series 72 ± 3% of the total of 209 children who were found to have esotropia and/or amblyopia had an abnormal refraction.

FAMILY HISTORY

A family history (Pratt-Johnson and Lunn, 1967) seems to be the only alternative to the detection of 'significant' refractive errors in very young children. In this series, a family history of squint or 'lazy eye' was present in only 58% (Table 9A $P < 0{\cdot}01$) of cases of esotropia (c.f. Molnar, 1967), and 52% (Table 9B $P < 0{\cdot}01$) of all cases presenting with esotropia and/or amblyopia.

REFRACTION VERSUS FAMILY HISTORY AS A MEANS OF SCREENING

The association of refractive errors with esotropia was statistically more significant than the association of a family history with esotropia:

	Positive	*Negative*	*Total*
Refractive error	97	40	137
Family history	79	58	137
	176	98	274

$\chi^2 = 4{\cdot}89$ D.F. = 1 $P < 0{\cdot}05$

If all children with esotropia and/or amblyopia are considered, the association of refractive errors is even more significant than a positive family history:

	Positive	*Negative*	*Total*
Refractive error	152	57	209
Family history	111	98	209
	263	155	418

$\chi^2 = 7{\cdot}47$ D.F. $= 1$ $P < 0{\cdot}01$

Furthermore, 35% of those children presenting, in this series, with something other than a 'visual problem' also had a family history of squint or 'lazy eye' (Table 10C). This suggests that if a family history alone was used to identify affected children, one third of all infants would have to be investigated in order to yield approximately half the total number of cases of esotropia and/or amblyopia. These figures are similar to those of Kornder *et al.* (1974). By comparison, the search for refractive errors would have to include the whole population, but it might give a higher yield (theoretically 72 ± 3%) of those destined to present with squint and/or amblyopia.

Although the ages of the children attending with 'non-visual' problems range from 0 to 15 years, this group might provide an indication of the incidence of hypermetropia or anisometropia in children. 20% of them (19 out of 91) had 'significant' hypermetropia and/or anisometropia. It is just possible, therefore, that 72 ± 3% of children with esotropia and/or amblyopia are to be found among 20% of our child population. For practical purposes, this compares favourably with 50 to 60% of children with squint and/or amblyopia being selected from 35% of the population with a positive family history.

On the basis of an overall incidence of 7% of children having squint or amblyopia, those with a 'significant' refractive error might be calculated to have a 1 in 4 chance of actually having squint/amblyopia, whereas the child selected on the basis of a positive family history could be calculated to have a 1 in 8·3 chance of being found to have squint/amblyopia.

It would, incidentally, seem wise to refract under cycloplegia all children who present to an ophthalmologist with a problem other than that of strabismus or amblyopia, since 1 in 5 of them may have a refractive error which is itself worthy of consideration.

SQUINT AND AMBLYOPIA PRESENTING WITHOUT A SIGNIFICANT REFRACTIVE ERROR

28 ± 3% of children who presented in this series with esotropia or amblyopia, or both, had no significant refractive error *at the time they presented.* Changes in refraction do occur as children grow (Brown, 1942; Ruskell, 1967; Slataper, 1950), but these changes may not be restricted to a simple increase or decrease in spherical hypermetropia. Therefore, the refraction found at the time a child presents with esotropia or amblyopia does not necessarily represent the situation at the time the esotropia and/or amblyopia were initially established (during the sensitive period?). Previous attempts to link ametropia, especially hypermetropia, with squint and amblyopia in a cause and effect relationship have never been conclusive (see, for example, Chavasse, 1930), perhaps because this simple possibility has not been considered.

Conclusion

This report demonstrates that the association between hypermetropia and/or anisometropia on the one hand and squint/amblyopia on the other hand is close enough to reconsider refraction as a basis for screening. Fifty years ago Thomson (1924) observed 'the squint is an outward sign—speaking of the majority of cases—that there is a refractive error. Not until the squint occurred, did the parents or doctor know that one eye was defective. . . . Our object and ideal should be the correction of the refractive error before the squint occurs. This ideal seems at the present moment impossible to reach on account of the obvious difficulty of examining children of pre-school age'. Is it?

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'Entente cordiale' in the early treatment of squint

R. PIGASSOU

'I regard as a highly satisfactory result a slightly anomalous type so that the condition represents a secondary form of microtropia' (Wybar, 1974).

'Guérir un strabique c'est lui donner une vision binoculaire normale; soulager un strabique c'est lui donner une union binoculaire esthétique (bien des signes fonctionnels dont se plaignent ces malades rendent inopportun le terme de soulagement). . . . L'union binoculaire est à notre avis un échec, la fusion périphérique est en réalité une correspondance rétinienne anormale, celle-ci est mise en évidence si on utilise un test convenable' (Pigassou *et al.*, 1975).

There is no doubt that Wybar's conception of the functional prognosis of squint does not coincide with our own point of view. How can we explain these two opposing viewpoints, formulated by two ophthalmologists described as 'strabologists'? Is agreement possible? In our opinion agreement is indeed possible—the early functional treatment of strabismus permits the unification of the two points of view.

In the first part of our text we shall present the reasons underlying the two opinions, and in the second part we shall expose some of the chief characteristics of early treatment.

I. The reasons for the divergent viewpoints

A. The two methods

Both authors express their opinion on the prognosis for squint based on the results obtained in children aged between 5 and 8 years and *treated by different methods*. Let us consider first of all the essential characteristics of these two therapeutic methods and their respective results.

THE ESSENTIAL CHARACTERISTICS

The so-called 'classical' method.—Treatment is the same whether correspondence is normal or abnormal; bifoveal stimulation is provoked (flash or massage) by means of a device such as the 'amblyoscope'. The sessions last from 20 to 30 minutes and take place two or three times a week over a period of 2 to 6 months. Between these sessions the child wears an optical correction with or without occlusion.

The prismatic method (Pigassou, Garipuy, 1973a).—Treatment is *different* according to the state of the retinal correspondence. If *retinal correspondence is normal*, the treatment consists of *exact prismatic correction*, which permits bifoveal stimulation at the patient's objective angle all day long. If *retinal correspondence is anomalous*, the treatment must first destroy the abnormal correspondence by the prescription of overcorrecting prisms; once the abnormal correspondence is overcome exact prisms are placed. The child wears his prisms constantly on his spectacles. If possible he undergoes binocular afterimage sessions with electronic flash (opto-multiflash).

THE RESULTS

The *classical method* is efficient, i.e., leads to binocular single vision, only in cases with underlying normal retinal correspondence, that is to say, in about 30% of cases. In the remaining cases it is not efficient.

The *prismatic method* can lead to binocular single vision in all cases of normal and abnormal retinal correspondence, only the alternating forms offering a less favourable prognosis. We say 'can lead' and not 'leads' as the technique is long and difficult; failures occur if the treatment is abandoned too early or if the instructions are not properly followed.

B. Since prismotherapy offers a more favourable prognostic and a wider range of application, why do so many ophthalmologists reject it?

We consider two main reasons to be responsible: the evolution of orthoptics; the difficulties encountered in prismotherapy. The *evolution of orthoptics* can be schematically divided into 3 periods.

FIRST PERIOD

The first period is that of the stereoscope: 'They date from the stereoscope originally introduced by Brewster in 1849 from Wheatstone's principles whereby the rays of light from two pictures were diverted by prisms. The original stereoscope was

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modified by Holmes in a simple clinical instrument wherein a convex lens before each eye was decentred to give the necessary prismatic deviation' (Duke-Elder, 1949). The principle of the stereoscope is to permit the fusing of different perspective images of the same object.

Remy's diploscope is used on the same principle. Diploscopic exercises may be divided into three stages: provocation of diplopia; establishment of simultaneous vision; establishment of stereoscopic vision (Cantonnet and Filliozat, 1932).

The aim of all these instruments is the same, i.e., to solicit binocular single vision. But their possibilities do not correspond to the theory underlying them, as there is no exact control of the objective angle. These enthusiastic attempts are short-lived, as they turn out to be ineffective, and the functional treatment of strabismus is thus abandoned for several years.

SECOND PERIOD

The second phase begins with the appearance of the amplyoscope (Duke-Elder, 1949). This instrument responds to more rational criteria, since one can carry out controlled stimulation at the objective angle. This method has become increasingly popular, and orthoptic units have been established in most countries and schools set up to train qualified technicians (orthoptists).

The aim of the treatment is to provoke not only a solicitation at the objective angle but also a bifoveal stimulation (by flash or massage).

Unfortunately the functional results are disappointing. Little by little orthoptic treatment is limited to cases of strabismus with underlying normal retinal correspondence, i.e., to 25 to 30% of cases. Sometimes orthoptic treatment is completely abandoned, since in cases of underlying normal retinal correspondence binocular vision develops spontaneously after surgery alone, when the operation re-establishes orthotropia.

THIRD PERIOD

The third period is marked by the importance given to the natural conditions of vision, both for examination and treatment. In the domain of *examination methods*, the first innovation is Bagolini's striated lenses associated with the filter bar. Then other methods appear—Pigassou's stereoprojector in polarised light, Aulhorn's phase haploscope (Pigassou, Aulhorn, and Bagolini, 1973).

So far as therapeutic methods are concerned, several techniques are intended to treat squint in conditions of free space (slight prismatic overcorrection by Bagolini, Lavat's objective angle in free space, Hugonnier's appreciation of diplopia). These different techniques have been described at length by their respective authors and we shall not develop them here. We shall recapitulate briefly the prismatic method, which is the method we practise.

When *retinal correspondence is normal* we use *exact prisms*. When *retinal correspondence is abnormal,* we use *overcorrecting prisms.*

Prismatic overcorrection of about 15 diopters with switch of fixating eye is the result of long experience and has been successively modified. It was clinical results (secondary postoperative divergence) which led us to practise prismatic overcorrection (Pigassou and Garipuy, 1963). The three main characteristics of the technique are the following: it is preoperative; it entails the placing of a prism of 15–20 diopters more than that necessary to place the patient at his objective angle; it changes the fixating eye.

Comments

We shall summarise the differing methods of the three periods.

FIRST AND SECOND PERIODS

1. Solicitation of single binocular vision in artificial conditions—the therapeutic development is—from single vision (first degree) to binocular vision (second degree); from fusion to stereoscopic vision (third degree).
2. The treatment is intended for squints with underlying normal retinal correspondence.
3. The therapy is effective only for the duration of the exercises.

THIRD PERIOD

1. Solicitation of binocular vision in natural conditions: only fusion tests are used, and tests of simultaneous vision and stereoscopic vision are used only for diagnostic ends.
2. The treatment is intended for squints with normal and abnormal retinal correspondence.
3. The therapy is effective all day long.

The difficulties of prismotherapy

The results obtained by prismotherapy are extremely favourable, but it is a difficult technique, demanding a great deal of rigour and precision and the exact execution of instructions. It is also a troublesome treatment, as it continues over one or two years.

It is precisely these difficulties which to our mind explain the hesitation of many strabologists to adopt the prismatic method, because it can only be successful in so far as one accepts its constraints. 'Few knowledgeable authorities doubt that it can be effective, but also few authorities believe that ordinarily the time and expense involved are worth the benefits to be gained' (Fleming *et al.*, 1973). This quotation from Fleming (who worked for four months in our clinic on a National Institutes of Health Research Fellowship Grant, USA) describes the attitude of American specialists, but reflects exactly the viewpoint of many strabologists. We are sure that they think that binocular union is a second-best solution, but they hesitate because of the difficulties involved in the length of treatment, etc.

II. Early treatment

A. The aim of early treatment

The justification of early treatment lies in the fact that binocular vision is a conditioned reflex which develops in the first years of life. Normal binocularity includes the motor pattern and binocular division, which are both developmental functions. During the period of elaboration of this sensory-motor binocularity, a perturbation may upset the developmental mechanism, and in consequence an insufficient or abnormal binocular function will take place. The characteristic feature of squint is the perturbation of binocularity, and we consider these sensory-motor perturbations to be adaptive processes.

Early treatment is intended: to eliminate the risk of abnormal adaptations or to destroy these adaptations before they become too deep-rooted; to permit the development of high-quality binocular vision, since it will have been formed during the period of cortical plasticity.

B. The techniques

We exclude from early treatment the therapy called 'deferred therapy,' which to our mind is not a true treatment but a delaying treatment carried out until the 'orthoptic age' is reached. This palliative treatment, if it prevents the development of abnormal retinal correspondence, is often responsible for alterations which are just as difficult to cure as abnormal retinal correspondence. In addition, when the functional re-education is finally begun, after 4 years of age, the plasticity of the cortex is already greatly diminished, and the binocular vision obtained is of less quality.

There are two types of early treatment: early surgery, and orthoptic treatment, sometimes with subsequent surgery.

EARLY SURGERY

Early surgery is intended to permit the development of normal binocularity. However, the results do not always correspond to the desired goal, because, even if the surgical intervention is correctly carried out, postoperative orthotropia is maintained in only about 30% of cases. In the remaining cases we observe the development of a slight angle of anomaly, or binocular union (Weekers, 1962; Evens, 1971).

ORTHOPTIC TREATMENT

Orthoptic treatment has its place in the current therapy of all functional and developmental troubles. The principles are the same as those on which the treatment of the other functions is based, and in particular the troubles of general motricity. It is virtually possible to transpose the directives of Bobath on the early treatment of cerebral palsy to the early treatment of squint, keeping in mind that in cerebral palsy there are organic lesions and that in squint in normal children the perturbation has a functional origin.

'Early treatment is important because of the great adaptability and plasticity of the infantile brain' (Bobath, 1963). 'The learning of movements is entirely dependent upon sensory experience, upon sensory output which not only initiates but also guides motor output' (Bobath, 1967). 'Sensori-motor deprivation may cause mental retardation in children whose mental endowment may be normal' (Bobath, 1971).

We shall not describe here the technique itself, which differs from that applied between 5 and 8 years, as it has already been discussed in various communications (Pigassou, 1973, 1974a, 1974b). We shall simply indicate the conditions essential for the successful outcome of treatment. These are: the collaboration of the parents; the preliminary apprenticeship of the child before the examination itself (this is carried out by the parents); the adaptation of examination methods and treatment to the intellectual and sensori-motor capacities of the child; the training of the orthoptist to these new techniques, child psychology, etc.

Here briefly are some indications concerning these points:

The collaboration of the parents

All parents who bring a strabismic child to us for treatment receive an explanatory leaflet on squint, the aims of the treatment, the reasons underlying the instructions, etc. Parents whose child is under 3 years of age receive the leaflet appended to this article (Appendix 1).

The preparatory apprenticeship

Provided we take into consideration certain imperatives (maturity, motivation, repetition, etc.) the child can, by carrying out the appropriate exercises, become capable of doing certain tests. All objective or subjective examinations are possible earlier than they normally would be if the child has previously carried out these preparatory exercises (an older child would answer these questions easily, as everyday sensori-motor experience would have naturally prepared him for them). These preparatory exercises are intended to prepare the child for a specific examination. To be effective they should be short and repeated frequently throughout the day, which is why we entrust them to the parents. We have established separate leaflets for each kind of practice exercise. As an example, we append the leaflet for the cover test to this article (Appendix 2).

The adaptation of the examination methods to the child's capacities

The examination of visual acuity can be carried out as early as 12 to 18 months, the time depending on the child's development and whether the tests are adapted to his cognitive and sensori-motor capacities. At this age Sheridan-type matching tests, which demand comparative visual exploration between two drawings, are difficult. 'The matching technique is not always possible between 2 and 4 years: the child may refuse to see the similarity between the two drawings, because these objects, whilst identical, are different' (Piaget, 1945). Tests which depend on orientation are impossible (Snellen or Landolt types) as the child does not yet distinguish left from right.

We have created a *visual acuity chart* for the examination of infants under 3, using drawings most frequently represented in nursery schools and which the child names in his own language (Fig. 1). 'This verbal approach is possible for the small child, as it corresponds to the laws of perceptive and cognitive development and precedes the matching capacity. In fact the mental process which leads to matching has its origin in the perceptive appreciation of a situation which in the normal child is necessarily verbal, thus explaining the predilection which children have for talking' (Duche, 1971). This method thus corresponds to the psychological and sensori-motor experience at this age and creates the optimum conditions for a correct answer.

The cover test, the examination of ocular motility, etc., demand sustained concentration on a precise object, and, as Jampolsky has emphasised, it is therefore essential that the object attract the attention of the child. To attract and more especially to sustain the interest of a baby of 1 year old, change or movement is necessary. We know that a motionless object in our visual field does not spontaneously attract our attention, whereas a moving object or the sudden appearance of a new object will attract our gaze. These facts are well exploited in publicity (signs with changing colours, flashing lights, etc.).

Since it is difficult to make the infant obey our instructions, we must make use of these reflexes to incite fixation, following movements, etc. To this end we have created certain objects specially adapted to the problem, e.g., flashing light in a doll's mouth (Fig. 2).

Therapeutic methods

The constraints involved in treatment should be minimised as far as possible. Since the wearing of glasses is virtually always necessary, they must be perfectly adapted to the facial, and more particularly to the nasal, morphology of the child. With this in mind we have had appropriate frames made (Fig. 3).

The training of the orthoptists

The orthoptists must be trained by means of systematic examinations of normal babies, and also be familiarised with infantile psychology.

Results

The results are extremely satisfactory, since, although the figure appears extraordinary, it is true that 100% of cures are obtained in children correctly treated. In nearly every case it is the lack of co-operation of the parents which is responsible for treatments incorrectly followed. (We would like to point out that a considerable number of parents give up the treatment in the initial stages.) The sensori-motor examinations carried out at 4 to 5 years of age in children having undergone a well-conducted early treatment show that the retinal correspondence is perfectly normal.

This fact makes redundant the divergent viewpoints on the treatment of eccentric fixation and anomalous retinal correspondence, since, thanks to early treatment, we should encounter in the future neither eccentric fixation nor anomalous retinal correspondence.

Conclusions

The current disagreements on the treatment of strabismus in children of 5 to 8 years of age stem from a different conception of squint and thus from the use of different therapeutic methods. At present it is more and more accepted that the functional treatment of strabismus should be begun between 1 and 3 years of age, and not 5 to 8 years. This opinion is in line with current therapy of all developmental troubles.

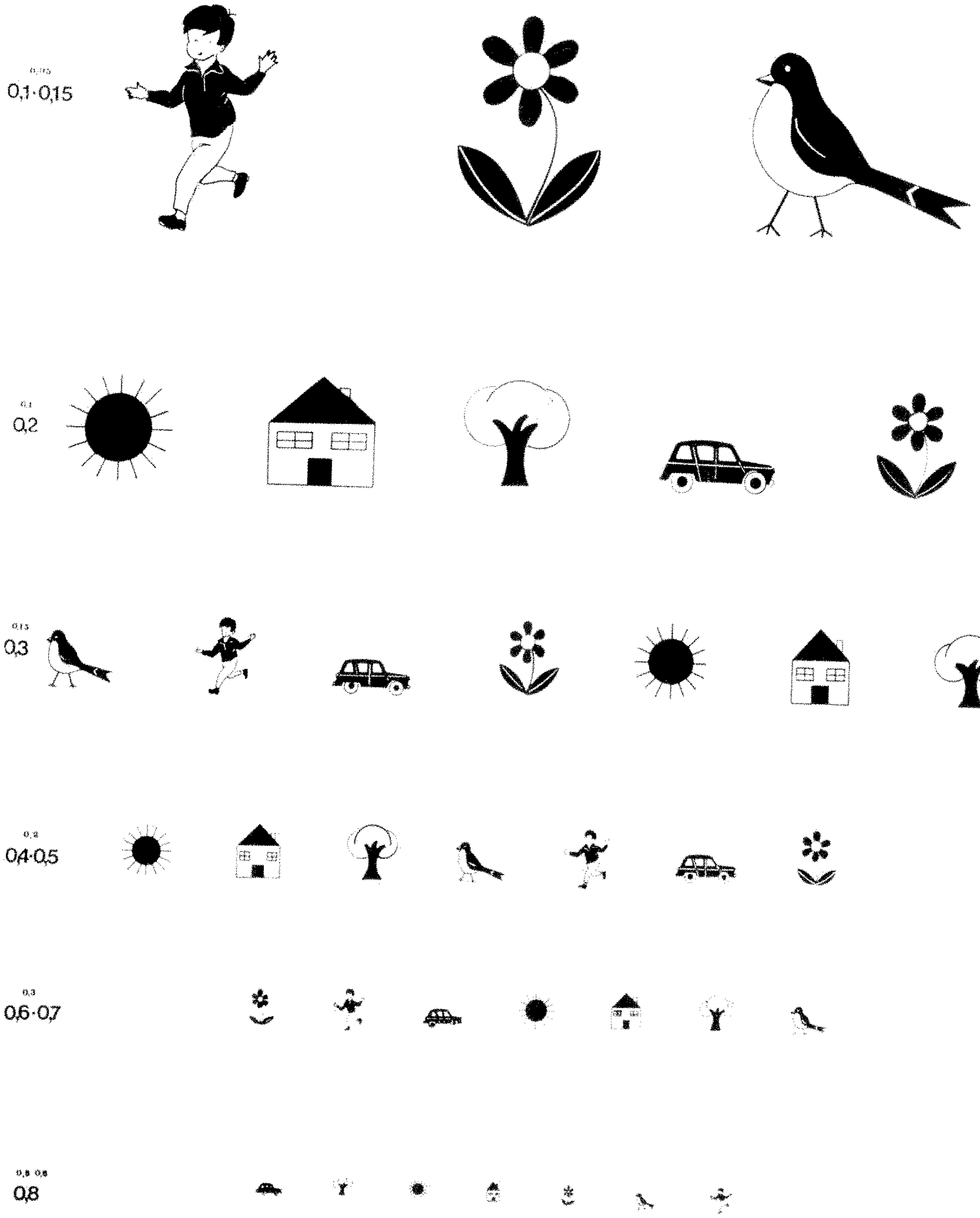


Fig. 1 *Visual acuity chart.*

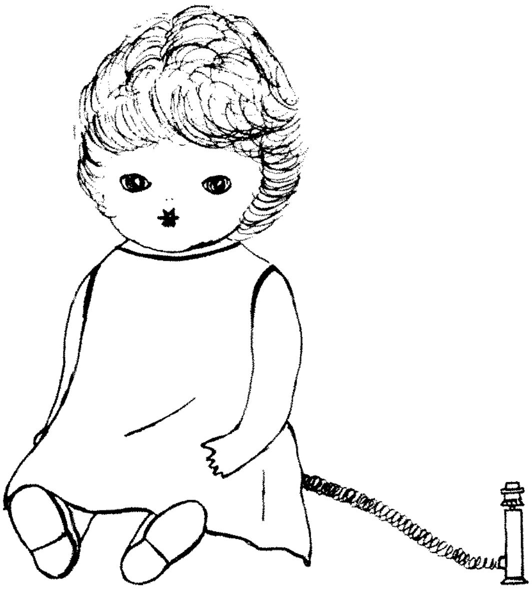


Fig. 2 *Doll with flashing light in mouth.*

Early treatment is possible only in so far as a system of early detection of squint is organised and in so far as appropriate techniques are applied. The extremely favourable results obtained by a treatment especially adapted to infants make it the duty of every ophthalmologist interested in strabismus to modify his methods and to treat the child as soon as possible after the diagnosis of strabismus can be pronounced.

Appendix 1: Parental role in the early treatment of strabismus

Your child squints: can something be done for him? The answer is *yes*, but on condition that you help us. The treatment can succeed only if the instructions we give you are followed—home exercises and medical control over one or two years. It is therefore pointless to begin treatment unless you are determined to accept these imperatives.

Your participation falls into two categories:

Firstly, our *therapeutic instructions* which must be conscientiously carried out in order to obtain a positive result.

Secondly, there are *preparatory exercises* which your child must master so that we may subsequently carry out certain necessary tests. Each of these exercises will be first of all carried out in your presence; the leaflet we give you corresponding to the exercise is intended to help you memorise it.

During the preparatory exercises you must realise that a child's potential is considerable, but to learn he needs to be helped. He will succeed more easily if you do not neglect certain educational principles:

You must encourage him, for he will be clumsy at the beginning.

It is only by means of the first clumsy attempts that he will arrive at the correct gesture.

You must not tire him out with too lengthy exercises. They should be short and frequent.

The preparatory exercises and therapeutic advice may differ depending on the case and the stage of development, and for this reason you must bring your child for *regular check-ups*. On these occasions we shall give you the correct guidance corresponding to your child's rate of progress.

Appendix 2: The cover test—Preparatory exercise

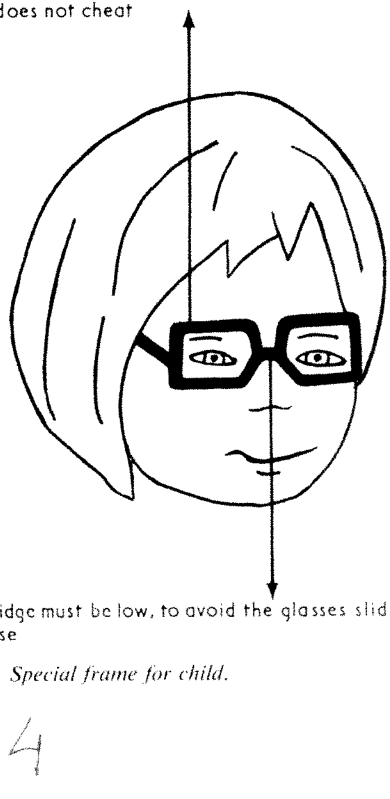
This examination is fundamental for both ophthalmologist and orthoptist, as it enables them to decide whether the child has a squint or not.

This leaflet is intended to explain to you the preparatory exercises to do at home so that we may carry out the examination as soon as possible.

The child should first of all fixate properly, i.e., he must maintain his attention for several minutes on the object he is asked to fixate, so that his eye does not stray. The object of fixation should be small, either a source of light or an object with a contrasting part (for example, of different colour), this contrasting part being small enough to serve as a point of fixation.

When the child has learned to fixate properly, he has to learn two things:

He must accept that you cover one eye with your hand



The frames must come up above the eyebrows, so that the child does not cheat

The bridge must be low, to avoid the glasses sliding down the nose

Fig. 3 *Special frame for child.*

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or a suitable object without turning his head or removing the hand.

He must continue to fixate (or start to fixate) the object with the free eye when the other eye is covered.

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Late reoperations for squint

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SUMMARY Ten patients in the age range 2 to 22 years are described who had operations initially for squint in childhood. Nine had had concomitant convergent strabismus and one divergent. All presented again in adult life with a cosmetic complaint, but two also had diplopia. Reoperations were done, age range 14 to 43. These ten were all the 'late reoperations' for squint which were done during the four year period 1972 to 1976 by one consultant (C.I.P.).

Technically these late reoperations were not difficult, though the amount of change predictable in position of the eyeball could be only approximate. Recession ± advancement ± resection of horizontal recti were done in all cases. In one case no medial rectus was identified attached to the eyeball; a mass of tissue behind the caruncle was mobilised and sutured to the globe with resultant good movement. To avoid tethering of the eye by scarred conjunctiva, vertical conjunctival incisions were often converted at suturing to ⊢ or ⊣ shaped wounds.

The absence of any new cases of diplopia (the two who had it preoperatively retained it without aggravation) is attributed to the fact that all cases were under-corrected, i.e., no convergent or divergent squint was converted into a divergent or convergent squint respectively, so that the non-corresponding image remained within the area of suppression, which probably extends only to the vertical meridian in a squinting eye.

Although there is considerable information about initial surgery for cases of strabismus and its results, surprisingly little seems to have been written about the problem of reoperation in adult life to correct those squints which have followed operations performed usually many years previously (Jampolsky, 1975). In the last 4 years 10 such cases have been operated on successfully; the result of this group is presented partly to encourage the publication of larger series which would help clinicians to formulate clinical judgment especially regarding operation. (We have excluded cases of secondary squint *not* operated on because of the difficulty in tracing their records: the decision against operation was based primarily on the absence of sufficient cosmetic disability, often related to the fact that they occurred in the elderly.)

From previous experience we had reached the tentative conclusion that the risk of diplopia following late reoperations is much less than perhaps tradition has suggested, and this conclusion is confirmed.

Material and methods

The 10 patients came from one consultant's 'routine' ophthalmic clinics held twice weekly in this hospital between 1 October 1972 and 1 April 1976. All had been referred by their general practitioners (to whom some had been sent by their opticians) with one exception, who was referred by a psychiatrist. Most came from Edinburgh or nearby towns. The preoperative details are shown in the Table and also the operations which were done.

Though measurements from limbus were used as an orientating base-line at operation, the amount of recessions and resections shown in the Table are from site of insertion actually found at operation. To conserve as much functioning muscle as possible whip sutures were inserted, in the case of (re) recessions or advancements, at the extreme anterior end

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Serial no.	*Sex*	*Details of initial operation(s)*				*Details of reoperation*	
		Diagnosis	*Age (years)*	*Operation(s) done*	*Presenting complaint*	*Age (years)*	*Diagnosis*
1	F	LCCS	11	RMR recession RLR resection LMR recession LLR resection	Cosmetic	43	LCCS/ACCS FR + 16° R/L 10$^{\Delta}$ FL + 17° R/L 10$^{\Delta}$
2	M	LDS	22	LLR recession LMR resection	Cosmetic	29	Moderate LDS −20° (L high myopia and open-angle glaucoma)
3	F	LCCS	13	LMR recession ? LLR resection ?	Cosmetic	29	LDS −16° with L eccentric fixation
4	F	RCCS	8	RMR recession RLR resection	Cosmetic	23	RDS FR −15° L/R 2$^{\Delta}$ FL −16° L/R 4$^{\Delta}$
5	F	LCCS	6	LMR Tenotomy Advancement of LLR	Cosmetic	21	LDS −30° L/R 12$^{\Delta}$ with eccentric fixation
6	M	LCCS	2½	LMR recession LLR resection	Cosmetic	20	LDS −15°
7	F	LCCS	4/5	LMR recession ? LLR resection	*(a)* Diplopia, looking down *(b)* Cosmetic	19	LCCS FR + 13° L/R 1$^{\Delta}$ FL + 13° with vertical diplopia
8	F	RCCS	2	RMR recession	*(a)* Diplopia *(b)* Cosmetic	14	RDS −20°
9	M	LCCS	4 8 9	LMR recession and LLR advancement 'Correction of LDS' Recession of each LR	Cosmetic	17	LDS/ADS −25°
10	F	ACCS	18	RLR recession RLR resection	Cosmetic	39	ACCS FR + 35° L/R 2$^{\Delta}$ FL + 35°

of the muscle (often along with a central suture); in resections the extreme edge was also used, and at least one supplementary central suture was inserted.

In general in recessions of medial recti Dacron sutures were used, while resections of medial recti and all operations on lateral recti had 6/0 chromic catgut sutures.

Results

These are shown in the Table. The results were recorded between one and three years after the reoperation.

Discussion

INDICATION FOR OPERATION

Several patients had postponed attending their own general practitioner for several years through shyness and were relieved to find sympathy for their cosmetic problems and a willingness to operate again. As occurs in other cosmetic problems, patients are often diffident about admitting embarrassment from cosmetic defects, which it may well be wise to elicit by a leading question. Each was warned that there was a risk of postoperative diplopia but that it was not great and was worth taking for the highly probable cosmetic benefit.

Patients were always warned that an ideal result was not guaranteed and that a further operation might be necessary, because the amount of change in position of the globe was difficult to predict from interference with previously operated muscle, and that an aim was usually slight undercorrection to minimise the risk of diplopia (and because even a slight overcorrection might be cosmetically unacceptable to a patient and his society who had become accustomed to the existing cosmetic defect).

OPERATION

A *provisional* decision was made preoperatively about the amount of recession and/or advancement to be done on the basis of the type of squint and initial operation presumed or known to have been present or done in childhood. That decision was always modified if necessary by the actual findings at operation.

Technically the operations themselves were not difficult—hardly more so, if at all, than initial squint operations. Even greater care than usual was taken to prevent perforation of the globe, especially when a heavily scarred muscle with adhesions extending posteriorly was mobilised. Tenon's capsule was usually represented by rather thin scar tissue easily separated from muscles. Thinned conjunctiva often overlay operated muscles, and in order to prevent

VA				
RE	*LE*	*Reoperation (measurement from site of insertion found)*	*Postoperative diplopia*	*Remarks*
6/6	6/60	LMR recessed by 5 mm	None	Cosmetically good FR +4° R/L 7^{Δ} FL +4° R/L 5^{Δ}
6/6	No PL	LLR recessed by 5 mm	None	Cosmetically very good LDS –4°
6/6	6/60	LMR not found. Tissue behind the caruncle mobilised and attached to sclera 7 mm behind limbus	None	Cosmetically very good; adduction possible: L eye can look straight ahead, but rest position –5°
6/6	6/6	RLR recessed by 8 mm	None	Excellent cosmetically RDS –5°
6/6	CF	LLR recessed by 5·5 with L Inf R resection 5 mm	None	Cosmetically very good LDS –4° and L/R 2^{Δ}
6/6	6/60	LLR rectus recessed by 9 mm	None	Cosmetically very good LDS –5° to –10°
6/6	6/12	LMR further recessed by 3 mm LLR resection 3 mm	As before the operation	Cosmetically very good LCS +4°
6/24	6/6	RMR resection 3 mm with advancement to original insertion RLR recessed by 6·5 mm	Present but in six months patient learned to ignore it	Cosmetically very good RDS –5°
6/6	6/6	LLR recession: 7 mm LMR resection 7 mm with advancement to original insertion. Two epithelial implantation cysts removed	None	Cosmetically excellent LDS –5° to –10°
6/6	6/6	LMR recession 6·5 mm LLR resection 7 mm	None	Good ACCS +6°

tethering of the eyeball by conjunctiva on the side of a recession, the vertical or curved conjunctival incision, made far behind the limbus, was converted into —┤, the horizontal part pointing posteriorly. *Interrupted* catgut (6/0 plain) sutures were used for all conjunctival incisions as in all cases of squint operated in this unit, to prevent 'granulations'. A search was always made superiorly and inferiorly, superficially and deep for stray muscle fibres.

In all cases the squinting eye (or maximally squinting eye in alternators) was operated on, though Folk (1973) has suggested that the previously unoperated eye is preferable because the amount of effect of operation is more predictable.

One patient was of particular interest (No. 3). No sign of even a remnant of medial rectus could be found attached to the eyeball. A search was made behind the caruncle as advised by Lyle (1952). Although no muscle was actually identified, the 'wadge' of tissue behind the caruncle was mobilised and (re) attached to the globe with resulting good movement—which confirmed the presence of muscle, with an insertion presumably not far behind the level of the caruncle.

Postoperative diplopia is the greatest cause of anxiety in these late reoperations. However, our clinical impression is that it is less common than is usually feared. *The only two cases in this series also had diplopia before this late reoperation.* This may be the result of our deliberate policy of (slight) undercorrection of the squint, i.e., to avoid shifting the image of the squinting eye across its vertical meridian (see Posner and Schlossman, 1951). If that is a valid principle and explanation for the avoidance of postoperative diplopia, the reason may be that half the retina with the aberrant image may be suppressed (hemiretinal suppression, Jampolsky, 1955). Similarly a horizontally oval area of suppressed retina may well be unlikely to extend (far) across the vertical meridian of the retina (Jampolsky, 1955).

CAUSES OF CONSECUTIVE SQUINTS

Most cases have a simple explanation, at least superficially, namely, too small or too large an amount of recession or resection at the first operation to make the visual axes straight (for distance). Some cases, however, seem to have been adequately corrected at the first operation in early childhood, so that presumably the absence of binocular vision allowed whatever small residual angle of squint may have remained after initial operation to increase gradually in subsequent years. It is surprising that a very small divergent squint resulting in childhood from operation for a convergent squint does not 'startle' the central nervous system by diplopia into recovery of binocularity. This failure may be due to too large an overcorrection which cannot be overcome, or more often too long an absence of binocular vision before initial operation, though Taylor's (1973) remarkably good results of operation up to two and a half years of age in congenital squints would not support that latter suggestion.

Although our postoperative results observed from 1 to 3 years afterwards are very satisfactory, it may be that over future years an increase in the deviation may occur with a need to consider another reoperation.

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Family distribution of concomitant squint in Greece

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SUMMARY From a study of a large number of brothers and sisters suffering from concomitant squint, the following data were obtained: (1) 42·9% of the patients showed congenital strabismus. (2) In 96·5% of the sibs strabismus was of the same type. (3) The presence of a significant refractive error occurred in 82·8% of the patients. (4) In all twins strabismus appeared at the same age in both twins, and the squint and the refractive error were of the same type. (5) The distance of the patients' homes from Athens had no effect on either (*a*) the time intervening between the onset of squint and the first visit to the eye specialist, or (*b*) the effectiveness of treatment.

Investigations to determine the genetic element in strabismus and the type of heredity involved have been the subject of numerous studies (François, 1961; Richter, 1967), although no definite conclusions have so far been reached. The present study does not aspire to offer a solution to this complex question and confines itself to an examination of familial cases of squint with the purpose of extracting data concerning: (1) The age of onset of squint; (2) the type of squint; (3) the frequency of the existence of a significant refractive error; (4) the incidence of amblyopia; and (5) the geographical distribution of squint in relation to the place of residence and its influence on (*a*) the period of time intervening between the onset of strabismus and the first ophthalmic consultation, and (*b*) the efficacy of the treatment.

Material and method

Our material, drawn from the archives of the Orthoptic Department, which contains about 12 000 patients, consists of 170 families containing 345 affected first degree relatives (brothers and sisters) who came under the observation of the Athens University Eye Clinic in the course of the last eight years. Cases of paretic strabismus or neurological syndromes were excluded from our study.

Information obtained from relatives suggested that the incidence of a family history of squint was ·55%. As we did not consider these data absolutely reliable, we have included in our group of patients only those that were under observation and treatment for strabismus for a considerable length of time. Our patients included five pairs of twins (10 persons), one pair being uniovular.

The patients were subjected to examination for the following data: (1) Personal and family history; (2) visual acuity, and refractive error determined after the instillation of atropine for 3 days; (3) type and angle of squint; (4) state of binocular vision; (5) fundus of the eye and type of fixation; and (6) place of residence.

Furthermore, patients were treated appropriately in each instance by: (1) Prescription of glasses; (2) occlusion; (3) orthoptic treatment; (4) surgical treatment.

Results

1. AGE OF ONSET OF SQUINT

The onset of strabismus in the 345 patients occurred: (*a*) Within the first year of life (congenital strabismus) in 148 patients (42·9%); (*b*) after the first year of life in 197 patients (57·1%). Out of the 148 patients with congenital strabismus 62 (42%) patients had a brother or sister affected with squint at a more advanced age, while the remaining 86 patients (58%) were brothers or sisters whose strabismus deveoped at the same age (congenital). In this latter group were 38 families with two children (including three pairs of twins), two families with three children, and one family with four children suffering from squint.

Of the 197 persons in whom strabismus appeared after the first year of life 107 (54·3%) were brothers or sisters in whom the onset of squint differed by more than a year, while the remaining 90 persons

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(45·7%) were brothers or sisters in whom the time difference in the development of squint was less than a year (among them two pairs of twins, one being uniovular). Thus out of the total number of 345 patients 176 (51%) developed strabismus at the same time as their brother or sister.

It is interesting that strabismus in the uniovular twins developed at the age of 3 years, and that one of the children had been adopted when 3 months old by a well-to-do family.

2. TYPE OF SQUINT

The diagnosis of squint was made when one of the following was demonstrated by a cover test: (*a*) Manifest deviation; (*b*) exophoria over 9Δ; (*c*) esophoria over 7Δ; (*d*) hyperphoria (including the alternating type). A convergent strabismus was found in 279 patients (81·2%) and a divergent strabismus in 66 patients (18·8%). Among the total, 12 had a sib showing a different type of squint—i.e., one sib had a convergent squint and the other a divergent one. The rest of the patients showed the same type of strabismus (96·5%).

All the twins had a convergent squint; in three pairs of twins it was uniocular, involving the same eye in both sibs; in one instance it was of the alternating type in both sibs; and in one pair it was uniocular, involving the right eye in one sib and the left eye in the other.

3. REFRACTIVE ERROR

The refractive error was considered significant in all cases featuring: (*a*) Hypermetropia exceeding 3 D; (*b*) myopia of any degree; (*c*) astigmatism over $\frac{1}{2}$ D; (*d*) anisometropia over 1 D.

On the strength of these criteria, a significant refractive error occurred in 285 patients (82·8% of the total number). In the five pairs of twins, the refractive error was found to be similar in each sib.

4. PRESENCE OF AMBLYOPIA

In 173 of the patients (50%) amblyopia was present at the first examination.

5. GEOGRAPHICAL DISTRIBUTION

The distribution of our patients with regard to their place of residence is shown in Table 1. In Greece there exist up-to-date orthoptic departments both in Athens and in Salonica, and thus our patients mainly come from the southern parts of the country.

To evaluate the effect of the distance of the patients' home from our orthoptic centre on their management we have taken into account two factors: (*a*) The time intervening between the onset of squint and the first ophthalmic consultation; and (*b*) the results obtained by occlusion in the treatment of amblyopia.

With regard to the time between the onset of strabismus and the first ophthalmic consultation by the patient, 49·8% of the patients (172 out of a total of 345) consulted an eye specialist within three years, and 23·48% of the patients (81 out of a total of 345) had their first consultation within one year of the onset of strabismus. From Tables 2 and 3 it will be seen that these percentages remain almost

Table 1 *Geographical distribution of patients with regard to place of residence*

Place of residence	*Number of patients*
Nomos Attica (Greater Athens and Piraeus)	154
Mainland Greece (except Nomos Attica)	29
Epirus	15
Thessaly	34
Peloponnese	50
Euboea	10
Crete	22
Aegean Islands	21
Ionian Islands	10
Total	345

Table 2 *Geographical distribution of patients presenting themselves for the first examination within three years after the onset of squint*

Place of residence	*Number of patients*	%
Nomos Attica (Greater Athens and Piraeus)	78	50·65
Mainland Greece (except Nomos Attica)	14	48·28
Epirus	7	46·67
Thessaly	17	50
Peloponnese	25	50
Euboea	5	50
Crete	11	50
Aegean Islands	10	47·62
Ionian Islands	5	5
Total	172	49·8%(± 1·1)

Table 3 *Geographical distribution of patients presenting themselves for the first examination within one year after the onset of squint*

Place of residence	*Number of patients*	%
Nomos Attica (Greater Athens and Piraeus)	39	25
Mainland Greece (Except Nomos Attica)	7	24·1
Epirus	4	26·7
Thessaly	8	23·5
Peloponnese	13	26
Euboea	2	20
Crete	6	27·3
Aegean Islands	5	23·8
Ionian Islands	2	20
Total	81	23·48% (± 3·7)

Table 4

Place of residence	*Number of cases of amblyopia*	*Results of treatment*					
		Visual acuity 10/10		*Visual acuity 7/10–9/10*		*Visual acuity <7/10*	
		Patients	*%*	*Patients*	*%*	*Patients*	*%*
Nomos Attica (Greater Athens/ Piraeus)	77	46	59·7	12	15·6	19	24·7
Mainland Greece (except Nomos Attica)	15	9	60	2	13·3	4	26·7
Epirus	7	4	57·1	1	14·3	2	28·6
Thessaly	17	10	58·8	3	17·7	4	23·5
Peloponnese	25	15	60	4	16	6	24
Euboea	4	2	50	1	25	1	25
Crete	12	7	58·3	2	16·7	3	25
Aegean Islands	12	7	58·3	2	16·7	3	25
Ionian Islands	4	2	50	1	25	1	25
Total	173	102	59% (±5·7)	28	16·2%(±6·3)	43	24·8%(±2·1)

constant irrespective of the place of residence of the patients.

With regard to the results of treating amblyopia by occlusion, it was ascertained that out of a total number of 173 patients: a visual acuity of 10/10 was obtained in 102 patients (59%); a visual acuity between 7/10 and 9/10 was obtained in 28 patients (16·2%); and a visual acuity of less than 7/10 was obtained in 43 patients (24·8%). Table 4 shows that these percentages remain more or less constant regardless of the distance of the patients' domicile from hospital.

Comment

The question whether squint is a genetically determined disorder has been much discussed. Richter (1967) states that the two types of hereditary transmission, autosomal dominant and autosomal recessive, are insufficient to explain the hereditary transmission of strabismus. Vogel and Krüger (1967) considered that strabismus is inherited in a multifactorial manner.

We believe that our study, based as it is on material with a marked family distribution, supports the hereditary nature of strabismus. 42·9% of the cases of squint were congenital, 51% of the patients developed strabismus at the same age as their brother or sister, and 96·5% of the brothers and sisters suffering from squint showed strabismus of the same type. In twins strabismus occurred at the same age in each sib.

The case of uniovular twins who both developed a squint at the age of 3 years in spite of growing up in different family environments from a very early age supports the view of Graham (1974) that environment has no effect on the occurrence of strabismus.

Pratt-Johnson and Lunn (1967) found a significant refractive error in 62% of their patients, as compared with 82·8% in our series. This high incidence of refractive errors probably occurred because our series consisted exclusively of brothers and sisters and thus emphasises both the hereditary nature of refractive errors and their connection with the occurrence of strabismus.

The geographical distribution of our material shows that the distance of the patient's home from Athens does not affect either the time intervening between the onset of squint and the first ophthalmic consultation, or the effectiveness of subsequent treatment.

We recommend to all parents that their other children should be examined once a squint has occurred in one child of the family.

The authors thank the orthoptist, Miss E. Koulopoulou, for her valuable assistance in the collection and processing of the material.

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Stereopsis and aniseikonia in uniocular aphakia

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SUMMARY Uniocular aphakia in the adult when corrected with a contact lens is in most patients no obstacle to binocular function. The long-term result is a balance between binocular function obtained and the comfort of the contact lens, and in this respect the advent of the soft lens, and especially the continuous-wear lens, appears to be most promising.

Over the past five years 46 patients attending Charing Cross Hospital with uniocular cataracts have been treated surgically and the vision has been corrected in the aphakic eye with a contact lens. The clinical impression gained was that the results were good, and all those patients that could be contacted were re-examined.

The aniseikonia in uniocular aphakia, when corrected with spectacles, is of such a magnitude that binocular function is severely interfered with. Various attempts have been made to reduce the aniseikonia. Thus Eggers (1937) showed that it was possible to reduce aniseikonia by inducing spectacle magnification in the phakic eye and reducing it in the aphakic eye by suitably varying the back vertex distance of the correcting spectacle lens. When substituting a contact lens for a spectacle lens the reduction in the spectacle magnification reduces the image size (Treissman and Plaice, 1946), as the nodal point of the system, contact lens and eye, moves back. Ogle *et al.* (1958) showed that the residual aniseikonia does not appear to be an obstacle to fusion. Although aniseikonia may vary from 4 to 10%, central or peripheral fusion can still be present, and the ability to fuse images when there is considerable difference in size may depend on the width of Pannum's areas (Burian, 1962). An alternative to the contact lens is the intraocular lens implant, which would be expected to reduce the aniseikonia even more than a contact lens, but even so it has been found that the aniseikonia may vary from 4% smaller to 6% larger in the aphakic eye and that the ability to fuse may also be variable, indicating that these appliances have little advantage over a contact lens (Troutman, 1962a, 1962b, 1963), although this point of view is contested by Choyce (1964). The results of treating children with uniocular aphakia with contact lenses is disappointing (Daniel, 1974; Binkhorst and Gobin, 1967), as too many children respond with suppression and squint. The absence of accommodation in the aphakic eye may play a part as suppression was more common in the younger rather than in the older children (Daniel, 1974).

Method

Patients were refracted with the contact lens in situ so that any residual astigmatism associated with the contact lens could be corrected and the best possible correction given to the other eye. All tests were then carried out with a trial frame containing the appropriate correcting lenses. Aniseikonia was determined by means of Ruben's aniseikonic plates and slides and the results were expressed as a percentage. Stereopsis was then measured with the Titmus Stereo-circles Chart, lenses were added to the trial frame to correct for the reading distance when required, and special care was taken to ensure that true stereopsis was being experienced rather than just blurring of the circles, which may occur at the 400″ and 800″ separations. The results were expressed as log stereopsis.

A group of 30 patients with different degrees of myopia but no other abnormality, all of whom had stereopsis, were used as a control group to determine if there was any relationship between stereopsis and aniseikonia. Aniseikonia was induced by correcting the less myopic eye with a soft contact lens (Sauflon 70) and the more myopic eye with the appropriate correcting lens in a trial frame. Any residual astigmatism associated with the contact lens was also corrected with the appropriate cylindrical lens in the trial frame. By suitable selection of myopes of varying severity a wide range of aniseikonic measure-

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ments were obtained, as well as the stereopis for each respective case. All subjects had a visual acuity of 6/9 or better in each eye when corrected.

A third group of unselected patients attending for routine refraction were examined to determine whether stereopsis changed with age. There were two groups—30 patients aged 20 to 30 years and 30 patients aged 60 to 70, all with a corrected visual acuity of 6/9 or better, in each eye.

Results

An analysis of the contact lenses used during the period under investigation showed: Hard lenses 2; soft lenses 7; continuous wear 18; total 27. All of the 27 patients investigated had worn their lenses for at least six months, and no hard lenses were fitted after 1972. The continuous-wear lenses were all fitted in the last 18 months of the period. In those patients wearing the continuous-wear soft lenses no significant change was noted in aniseikonia or stereopsis over a three-month period. In all the patients a visual acuity of 6/9 in each eye was obtained.

In the myopic group of subjects a significant correlation was found between per cent aniseikonia and log stereopsis (Fig. 1). The regression line for log stereopsis on per cent aniseikonia, by the theorem of least squares, is drawn as a solid line; on either side of the regression are the 95% confidence limits in dotted lines, the inner lines for the regression line and the outer for the individual points. Aniseikonia greater than 19% was not obtained.

It was possible to measure aniseikonia in all 27 uniocular aphakics, but in two there was no demonstrable stereopsis on the Titmus Chart, circles or fly. The aniseikonia in these two patients was 25 and 29% respectively. In all the other patients the aniseikonia was below 20%.

No significant difference was found between the mean stereopsis for the two age groups, 20 to 30 years and 60 to 70 years.

The continuous-wear lenses were made of Sauflon 85 (poly (vinyl pyrrolidone × methyl methacrylate) 85%); of the daily wear lenses five patients had hydron lenses (polyhydroxyethyl methacrylate), and in two patients Sauflon 70 (poly (vinyl pyrrolidone × methyl methacrylate) 70%).

Discussion

In the myopic group of subjects on the assumption that per cent aniseikonia is the independent value and log stereopsis the dependent it can be seen from Fig. 1 that an empirical relationship does exist between the two, the correlation coefficient being 0·78. The results obtained were used to determine whether the uniocular aphakic group of patients compared in any way. It was initially hoped that a relationship between per cent aniseikonia and log stereopsis would be found in the uniocular group, but this was not the case, possibly because the aniseikonic measurements were bunched together. When the results from the uniocular aphakics are statistically tested against the myopic group it may be concluded that they come from the same statistical population (Fig. 2).

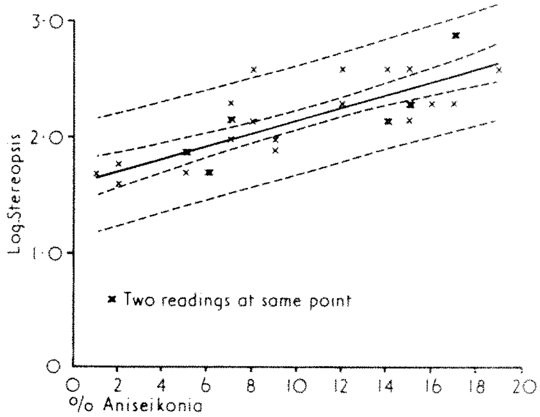

Fig. 1 *Log stereopsis plotted against induced per cent aniseikonia for the control of myopic group of subjects. The straight-line relationship is shown as a solid line, and the 95% confidence limits are shown as dotted lines on either side of the regression line. The outer dotted lines are the 95% confidence limits for the individual points*

Stereopsis was present up to an aniseikonia of 19%, but above this value central stereopsis probably breaks down, for in the two uniocular aphakic patients the aniseikonia was 25 and 29% respectively and no stereopsis was present on the Titmus Stereo-circle test. This is to be expected, for when looking at the results obtained from the myopic control group (Fig. 1) when aniseikonia is approaching 20% at best only a 400″ of an arc separation would be expected when testing on the Titmus Stereo-circle test. On fitting contact lenses diplopia was initially experienced in some of the uniocular aphakics but persisted only for some 24 hours. No improvement in aniseikonia or stereopsis was observed in any of the patients after wearing the lenses for three months.

One patient, a professional dancer with uniocular aphakia, was of particular interest. He had been unable to cope with his daily wear contact lens, for while dancing he experienced spacial disorientation

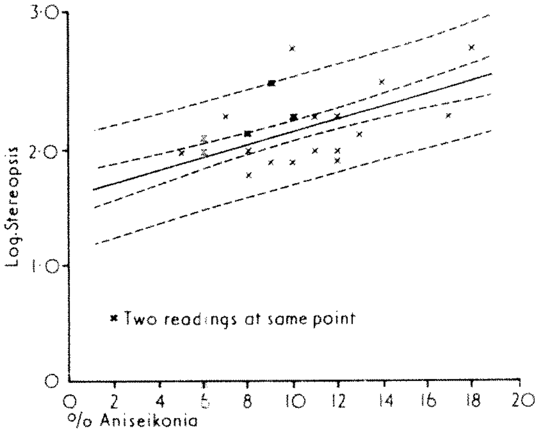

Fig. 2 *Results obtained from the uniocular aphakic group superimposed upon the regression line and 95% confidence limits obtained from the control myopic group of subjects*

owing to tilt of the horoptor. Between engagements advantage was taken to fit a continuous-wear contact lens, tilt of the horoptor was again initially noted, but within 24 hours he had adapted to his 14% aniseikonia, and spacial distortion was no longer experienced.

From Fig. 2 it may be seen that most of the results are bunched around an aniseikonia of 10%, which gives a very useful degree of stereopsis. Even the two patients without central stereopsis had some degree of binocular function and benefited from the improved peripheral field on the aphakic side. Thus, provided stereopsis was present prior to development of the cataract the results indicate that useful stereopsis will be present in most patients when correcting with a contact lens. The time of fitting does not appear to be important, as patients were fitted from two months to three years after surgery, though it must be pointed out this group of patients consisted only of adults. The results confirm a previous report (Nolan *et al.*, 1975) that it is worth considering a routine contact lens trial after cataract extraction and leaving the insertion of an intraocular lens implant as a secondary procedure.

Of interest is the trend towards soft contact lenses, as experience has shown that these are more comfortable and can be worn for longer periods than hard lenses. Even more important is the development of hydrophylic lenses with a manufacturer's claim of high oxygen permeability in order to permit continuous wear. With the evolution of more comfortable lenses it has now become apparent that a balance exists between the visual benefit obtained with a contact lens and the bother of handling, wearing, and caring for a lens. This is most clearly demonstrated when using continuous-wear lenses, as patient handling is eliminated and comfort is at an optimum. Further, as most soft lenses are a semi-scleral fit, stability is greater than with a small hard corneal lens, so reducing the prismatic effect that is commonly encountered. It would appear to be the rule that patients become readily accustomed to quite high degrees of aniseikonia, given a trouble-free contact lens.

Today there should be little hesitation in removing a uniocular cataract in the adult. It is suggested that after surgery there should be a contact lens trial, and the author's preference is to fit a soft rather than a hard contact lens provided the aniseikonia is below 20%. The type of lens chosen will depend on the patient's ability to handle a daily wear lens. In the elderly, or when the aniseikonia is greater than 14%, a continuous-wear lens is indicated as first choice. When the aniseikonia is greater than 20% a continuous-wear lens may be tried, but a patient in this category is probably a candidate for an intraocular lens implant provided binocular function is present. Continuous-wear lenses are not without complications (Highman, 1975). Thus out of 53 aphakic lenses thus fitted there has been corneal vascularisation (1 case), infection (1 eye), microcystic oedema (1 eye), and an 'acute red eye reaction' (5 cases). In spite of these complications none of the patients have been permanently stopped wearing their lenses. In children there would seem to be a case for overcorrecting by + 3 dioptres and giving spectacles for distance, because of the absence of accommodation.

I should like to thank Mr Arnott and Mr Higgitt for their help in allowing me to examine their patients for the above investigation. I should also like to thank the Governors of Charing Cross Hospital for their financial help and the Medical Illustration Department for the art work.

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Hydrophilic lenses for 'continuous' wear in aphakia: Fitting at operation

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SUMMARY This system of soft lens fitting in conjunction with the backward sloping corneal incision proved satisfactory in 84% of cases and provided good fill-in vision during the postoperative period —that is, until a decision about the type of long-term optical correction was made in each case.

The visual problems of aphakia are mainly due to the optical distortion produced by spectacle correction. Even with new aspheric forms difficulties arise from prismatic effects—ring scotoma, 'jack-in-the-box' phenomenon, and reduced field. For the monocular aphake there is also the absence of binocularity due to aniseikonia. Contact lenses of polymethylmethacrylate have done much to solve these problems, but they also introduce difficulties of visual instability, discomfort, and, more important in the older age group, difficulties in handling. Stability and comfort could be overcome by soft contact lenses for daily wear, but the handling problems are much worse. The cleaning process involved and the breakage rate are enough to discourage the most strongly motivated. A continuously worn lens would overcome all these problems.

All the usual arrangements for optical management leave the patient poorly corrected during the postoperative period, which is normally about six weeks. In order to fill this gap, aid early mobilisation, prevent postoperative confusion, and provide an alternative to the intraocular implant, it was decided to divide this trial into two parts—the first where a 'continuous' wear lens was fitted at operation, and the second, the more conventional, the fitting of these lenses definitively at six weeks.

The placing of a lens on the eye at operation was introduced because of the observed absence of inflammation in the early postoperative period, when a backward sloping corneal incision was used. It has often been suggested that this type of section would produce high degrees of corneal astigmatism. This has not been our experience (on average a spectacle astigmatism of 1·58 was found by analysis of 100 consecutive cases performed by both consultant and resident staff when this incision had been used). Increased astigmatism would seem to relate to those incisions that slope from the limbus towards the pupil. The other advantages of the backward shelving incision, such as good visualisation of the surgical field, minimal bleeding, and early reformation of the anterior chamber, are considerable. Details of this incision have been described (Pierse, 1975), but its main features (Fig. 1, colour plate) are: (1) Positioned superficially at the tips of the final loops of the precorneal vessels; (2) shelving back towards the angle of the anterior chamber; (3) 140° of arc; (4) closed by a 10/0 Perlon continuous suture with buried knots (Fig. 2).

The lens material used in both these trials was Sauflon 85, as this is the only material available that has an oxygen permeability that at optical lens thickness allows a near physiological volume of oxygen to reach the cornea (Larke, 1976). Lenses of two back curves were used, 7·8 mm and 8·1 mm, and the decision regarding which was indicated for a particular patient was taken from the results of a

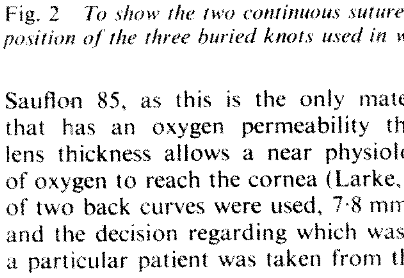

Fig. 2 *To show the two continuous sutures and the position of the three buried knots used in wound closure.*

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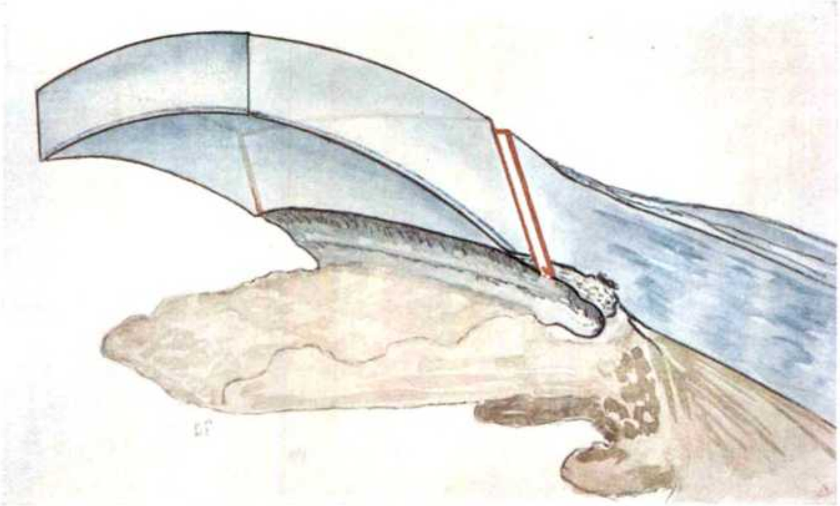

Fig. 1 (Pierse and Kersley) *To show position of backward sloping corneal incision.*

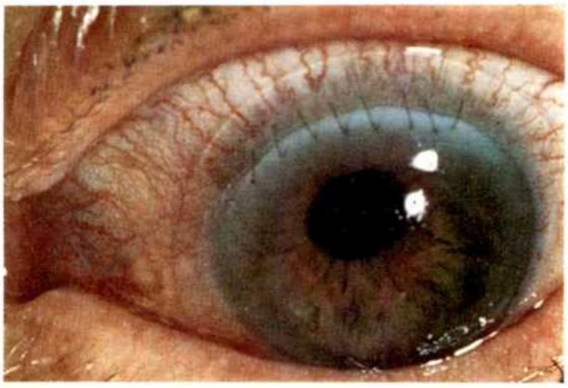

Fig. 3 (Pierse and Kersley) *Aphakic 'soft' contact lens inserted at operation and worn continuously; seen two days after operation.*

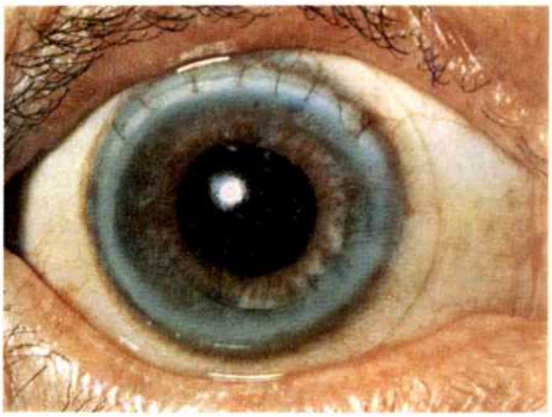

Fig. 4 (Pierse and Kersley) *Aphakic 'soft' contact lens inserted at operation and worn continuously; seen six weeks after operation.*

keratometric follow-up, carried out in this department, of patients before and after cataract extraction. This showed in the averaged graph a 0·4 mm flattening of the flattest K reading after the first postoperative day. This figure was therefore added to the flattest preoperative keratometry reading (the flattest reading being the one most commonly used in soft lens fitting), and the nearest of the two lenses available was then taken. The graph used was consistent with that shown for the majority of patients using conventional incisions (Floyd, 1951). The other parameters of the lenses used were: power +16·0 DS, diameter 13·50 mm, and front optic reduction to 8·0 mm. The power was chosen from the results of two previous trials (Bausch and Lomb and Sauflon 70) so that on average patients would be slightly overcorrected. The diameter was large enough to bridge the incision line and the front optic reduction small enough so that the transition did not rest on the incision.

The lens at the time of insertion looks very steep, having an air bubble between it and the cornea, but within the following few hours, with further reformation of the anterior chamber, the air bubble disappears. Eyes are not padded, so that on waking the patient can see. No antibiotic cover is given and no steroids are instilled unless there is a definite indication (Fig. 3, colour plate). Follow-up consists of daily slit-lamp examination until discharge and then weekly examination for a month, when refraction is carried out and a decision taken about future optical correction.

Of the 75 consecutive patients in this trial 25 were men and 50 were women, and their ages varied from 48 to 90 with an average of 72·9. They were selected at random from the clinics of the Croydon Eye Unit and the surgery was performed by both consultant and resident staff. All showed rather more corneal oedema than would have been expected without the lens, but this, and the mild striate keratopathy which lasted rather longer than usual, cleared in about seven days. No evidence of raised intraocular tension was found in the immediate postoperative phase. Twelve patients were not wearing their lenses six weeks postoperatively (Table 1). One was rubbed out, three had surgical anterior chamber problems, four had more oedema than was acceptable (of these, three had had unplanned extracapsular cataract extraction), and two had an acute uveitis of unknown aetiology that settled quickly with local steroids. Therefore of the trial group 3 (or 4%) had had problems that may have been soft-lens induced, but all settled on lens removal. 84% were still wearing their lenses at the time of decision about permanent optical correction.

Visual acuity has not been analysed, as it was not the intention of this procedure to aim at a definitive correction. However, all patients were pleasantly surprised at their early visual acuity and a few achieved as good an acuity with their operation lens as they did after refitting (Fig. 4, colour plate).

Keratometric follow-up of these patients is shown in two histograms (Figs. 5 and 6), the flatter meridia above the abscissa and the steeper below. In the first, the preoperative histogram, the ordinate has been drawn through 7·6 mm, as this is the average for the series and fits with the normal population curve. In the second histogram, the keratometry at six weeks, as one might have expected the two peaks have moved away from the ordinate in

Table 1 *Reasons for lens removal in the immediate post-operation phase (16%)*

No. of patients			
4	Oedema	Failed intracapsular extraction	2
		Failed intracapsular extraction with raised tension	1
		Aetiology unknown	1
3	Iris/anterior chamber complications	Incarcerated trauma at home	1
		Incarcerated in first 24 hours post-operation	1
		Shallow anterior chamber	1
2	Excessive uveitis		
1	Old fundus haemorrhage (i.e., no visual improvement)		
1	Lost lens		
1	Previous monocular aphake—happy with her glasses		

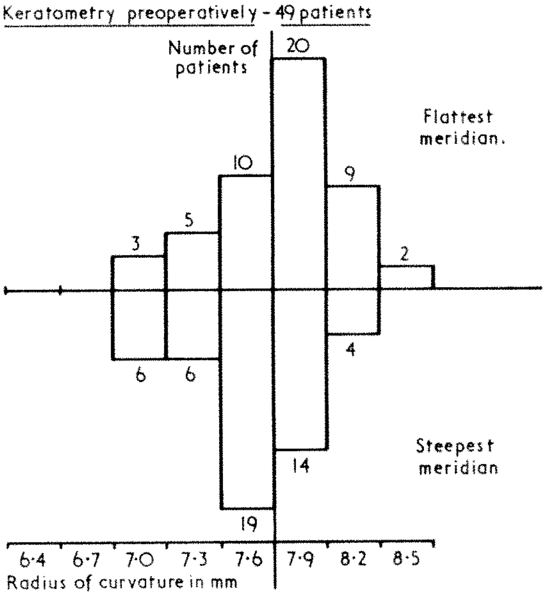

Fig. 5 *Preoperative keratometry.*

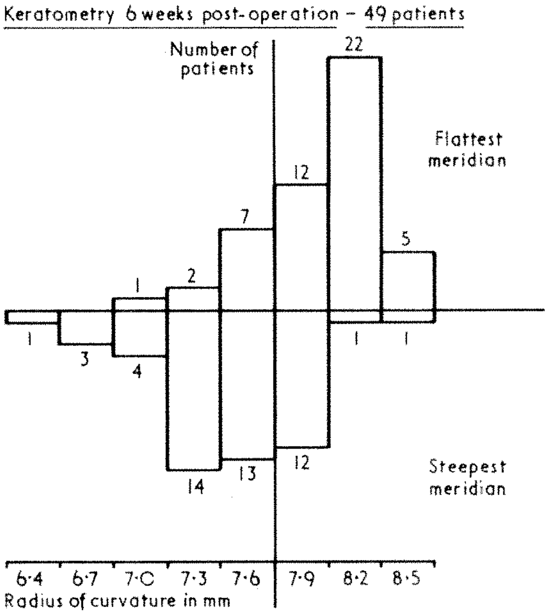

Fig. 6 *Postoperative keratometry.*

opposite directions, showing the development of corneal astigmatism. This is the same pattern as that found without soft lenses; therefore it is suggested that the normal postoperative corneal progression is not affected. Five lenses were removed at the end of the six-week period, and this confirmed that the keratometries did not alter.

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British Journal of Ophthalmology, 1977, **61**, 38–42

Hydrophilic lenses for 'continuous' wear in aphakia: Definitive fitting and the problems that occur

H. JONATHAN KERSLEY, CHRISTOPHER KERR, AND DERMOT PIERSE
Croydon Eye Unit

SUMMARY Patients have been very satisfied with these lenses (78% wearing at the end of six months), not the least those with reduced function of the macula. The problems of infection have been discussed, and apart from improvement in lens materials patient selection is of paramount importance. The problem of deposits is presented, but their elimination will depend on more research into their nature and development, improvement of the material's resistance to this form of attack, and improved lens design to overcome corneal and tear flow problems.

This is a clinical study of 50 patients fitted with soft lenses for 'continuous' wear at approximately six weeks after operation and their follow-up for six months. The advantages of corneal contact lenses in aphakia mentioned in the first article (above) also apply broadly to soft lenses. However, previous studies with soft lenses for daily wear have shown their limitation.

The conclusions from a trial with the Bausch and Lomb Soflens for daily wear (Kersley and Gasson, 1975) were that the stock system of supply worked well in hospital practice, that the lens was fairly well tolerated even in corneal contact lens failure, but that the spin casting method of manufacture lacked the flexibility of approach to fitting that was desirable, the handling of lenses was difficult, the visual acuity less than with spectacles (an average of 0·51 lines), and the breakage rate unacceptably high (three lenses per patient for six months).

When the higher water content lens (Sauflon 70) was tried for daily wear (Kersley, 1975) the conclusions were that the lens was better tolerated, the lathe-cut lens was better for fitting and gave better vision, but the lenses were less well reproduced, were more fragile (four lenses per patient per six months), and 'custom' making of lenses resulted in delay in supply.

From these two trials it will be realised that in aphakia the lens required needs to be: of high water content, lathe cut, fitted from stock, free from handling and breakage problems.

A 'continuously' worn lens would satisfy this last requirement, and the development of Sauflon 85 seemed to provide a material that could fulfil all the requirements of the ideal lens. Chemically the material is a cross-linked copolymer in which the comonomers are polymethylmethacrylate and vinyl pyrrolidone, compared with the HEMA based materials that are cross-linked homopolymers of hydroxyethylmethacrylate (PolyHEMA) and ethylene glycol dimethacrylate. Sauflon 85 has a water uptake of 85% and oxygen permeability of 900 units. This compares with the HEMA materials whose oxygen permeability is 40 units when the unit of oxygen permeability is $\frac{\text{cm sec cm}^2\ (\text{cmHg})}{(\text{cc } O_2 \text{ STP } 10^{-10})}$ (Larke and Hirji, 1974). The relationship is, however, not linear.

This, as mentioned in connection with the fitting at operation, even with the thickness of an aphakic lens allows a near physiological volume of oxygen to pass to the cornea with the lids closed. The other parameters of lenses used are the same as before (back optic radii of 7·8 mm and 8·1 mm, diameter of 13·50, reduced front optic of 8·0, and an average centre thickness of about 0·50).

Of the 50 patients in this series 41 had been fitted at operation (64% of the 'fitted at operation' series), and this raised the point that a decision had to be made during the postoperative period about the most appropriate optical device for a particular patient. This will receive more discussion later.

The fitting of these lenses was carried out at about six weeks after operation. After slit lamp examination, refraction, and keratometry a final decision was made as to soft lens fitting and a lens chosen from a stock of 44 lenses. The appropriate power had been calculated from the mean ocular

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sphere and the curvature chosen as that nearest to but not steeper than the flattest K reading. The lens was then inserted and left for half an hour so that the swell factor and temperature could adjust before the lens fit was assessed. At this time, as at all other assessments, particular attention was paid to centration, lens movement, over-refraction, and perilimbal vascularity. Our aim was to produce a slightly loose-fitting lens so that a 'tight' syndrome would not occur under adverse conditions.

At the end of this first visit the patient was given an explanation about what had been done and told of the necessity for attending regularly for follow-up. Lens handling being the major problem of soft lenses in aphakia, patients were not taught how to remove their lens but were all told to report immediately if redness, soreness, or reduced vision occurred.

The second visit was within 24 hours to check the absence of corneal oedema and reassess lens fit. The third visit was one week later, and thereafter patients were examined monthly. At these visits the following were recorded: visual acuity, over-correction, lens fit, slit lamp findings.

Overcorrections were given where indicated and reading additions prescribed. At the final visit keratometry was performed, the cornea stained with fluorescein, and the lens cleaned chemically and then heat 'sterilised'. The results are shown in Table 1.

Patients were never rejected on the grounds of poor central vision as these patients would be even more hampered by the added difficulties of aphakic spectacles (as previously described) and would find the handling of other contact lenses extremely difficult. In fact reduced central vision in aphakia may in itself be an indication for a continuously worn soft lens as a low visual aid.

Rejection of patients at the outset (Table 2) centred around high astigmatism, particularly when associated with good visual acuity or an established aphakic correction in the other eye. Those taken off the trial (Table 3) contain lens stability problems for the most part, one insuperable greasing problem, one surgical problem, and three were removed for social reasons.

The choice of lens radius was reflected in the average flattest keratometry (Table 4). The increased corneal astigmatism that occurs in aphakia accounts for our bias towards an apparently steeper fitting. Four radius changes were necessary during the trial—one flatter because of a tight lens edge and three steeper because of poor centration. Comparison of the flattest keratometry at six weeks and six months (Table 4) shows a general flattening (but not enough to affect lens fit), while the change in average mean keratometry shows the constancy of this figure that we had found before.

Table 1 *Results*

50 consecutive cases	100%
39 completed the trial	78%
8 taken off the trial	16%
3 rejected at outset	6%

Of those completing the trial:
Ages 34 to 90. Average 71 years.
Males 15 (39·5%). Females 23 (60·5%).

Table 2 *Patients rejected from the trial (3 cases)*

Peripheral corneal degeneration with vascularisation
High astigmatism; better visual acuity with glasses
High astigmatism; second aphakic eye of patient happily wearing spectacles

Table 3 *Patients taken off the trial (8 cases)*

Excessive greasing
Eye rubbing (deaf patient)
Unstable lens (eye rubbing)
Unstable lens (four lenses in two months)
Iris incarceration followed by increased intraocular tension leading to trabeculectomy
Left the area for India
Left the area and after two episodes of keratitis
Died

Table 4 *Keratometry during lens fitting*

		Average
Flattest reading at six weeks	7·1–8·5	7·76
Flattest reading at six months	7·1–8·4	7·89
Average of mean keratometry readings at six weeks		7·68
Average of mean keratometry readings at six months		7·72

Lenses given—20 of 7·8 (53%) and 18 of 8·1 (47%)

Table 5 *Ocular spherical correction for the series*

Maximum + 21·25	Minimum + 9·25	Average + 14·04

Average soft lens power prescribed + 15·12

Comparison of the ocular spherical correction and power of lens supplied (Table 5) shows the presence (between soft lens and cornea) of a –1·0 D liquid lens. This was considerably more than is usual in soft lens fitting and indicated the influence of lens rigidity and the semi-scleral fit (the aphakic lens being relatively thick) against the normal peripheral corneal flattening. It also confirmed our clinical impression that our fitting criteria did not result in an especially steep fitting lens.

The keratometric cylinder is shown (Table 6) to have the highest value, and a progressive reduction of this figure is found in the ocular astigmatism (back

Table 6 *Cylindrical correction*

			Average
Keratometric cylinder	Max. 8·62	Min. Nil	2·60
Spectacle cylinder	Max. 4·0	Min. Nil	1·70
Converted to ocular cylinder	Max. 5·62	Min. Nil	2·0
Average cylindrical spectacle overcorrection (all cases)			1·35

vertex distance corrected spectacle cylinder) and that required at contact lens overcorrection. Comparing those given with those not given overcorrections we had, as with other soft lenses, an acceptance of less than 2·0 D cylinder without an overcorrection. The average overcorrection cylinder prescribed was 2·43 D. The number of overcorrections given was 15 (39·47%), a higher figure than in the previous studies and may account for the good acuity (taking the best visions recorded) compared with spectacle refraction—both average at 6/9.

Technical problems lay in the specifications of lenses. The difficulties of checking soft contact lenses are well known. Therefore without extreme accuracy in production and reproduction by the manufacturers troubles will continue to occur. This problem exists to some extent with all types of high-power soft lenses. However, in this trial powers varied and, worse, cylinders were sometimes present. The troubles often seemed to lie in variations of overall thickness and consequent alteration in 'wrapping' from lens to lens. Nevertheless the represcribing of an overcorrection because a replacement lens was not the same as its predecessor is both expensive and depressing. Which was at fault, the first or the second lens? During the course of the trial this situation improved considerably, some patients achieving 6/6 vision at six months without an overcorrection (Fig. 1, colour plate).

Of the problems that occurred during the follow-up, assessment is most satisfactorily achieved by examining lens replacement, as no matter whether the problem was corneal or lens orientated the lens was removed and replaced. Thirty-six were replaced (or 1·94 per person per six months including the initial lens), a happier picture than with daily wear (three to four lenses per patient per six months). The vast majority of these were lost, broken, or changed because of deposits—some 75% (Table 7). Many of those with deposits might have been reclaimed by a cleaning/renovation process, thereby reducing the replacement rate still further to 1·42 per patient per six months.

The other important considerations are the infections. In this series there were four cases in which lenses were changed. Table 8 shows five cases, as the patient with the meibomian cyst had a very mild episode that was treated with antibiotics without lens removal. The first three are the serious ones. The first 'makes sense' in that corneal contact lens intolerance is well known with upper respiratory tract infections, and so one might expect a person using a continuous-wear soft contact lens to be at risk. The second brings up the problem of patients moved beyond our care and the increased susceptibility of those patients who produce deposits. The third is the most worrying, as it would seem to relate to something done to the lens by us, possibly the disturbance of a balanced tear film caused by the lens change. All these patients responded satisfactorily to treatment and are now again wearing their lenses.

Since the trial two patients have developed some degree of peripheral vascularisation and an attempt is being made to overcome this by having the lens made with a flattened peripheral curve in order to achieve more edge lift. Early observations suggest that this will work.

Deposits on these lenses are the greatest drawback to aphakic continuous wear, because once deposits have developed the lens becomes unstable, liable to contamination and infection, often uncomfortable, and certainly difficult to clean. In continuous wear the soft mucous deposits of daily wear have been replaced by discrete masses of rocky appearance that can coalesce to give large conglomerates (Fig. 2, colour plate). They are usually axial but do not necessarily start off that way, as a single dot once formed will tend to locate in the interpalpebral aperture, obstruct blinking, and develop axially.

The original formation of a deposit certainly relates to poor blinking over these lenses of great

Table 7 *Lenses replaced*

Lost	5	(14%)
Broken	10	(28%)
Deposits	12	(33%)
Radius change	4	(11%)
Power change	1	(3%)
Infection	4	(11%)
Total	36	(100%)

Table 8 *Infections: five cases*

1. Corneal ulcer and acute uveitis associated with 'flu' (faint nebula remaining).
2. Severe keratitis while on holiday abroad; patient prone to deposits (faint nebula remaining).
3. Small limbal abscesses with generalised keratitis—3 days—after a lens change because of deposits (*E. coli* cultured) (faint nebula remaining).
4. Conjunctivitis associated with a meibomian cyst.
5. Conjunctivitis—10 days after a lens change.

All patients again now wearing their lenses.

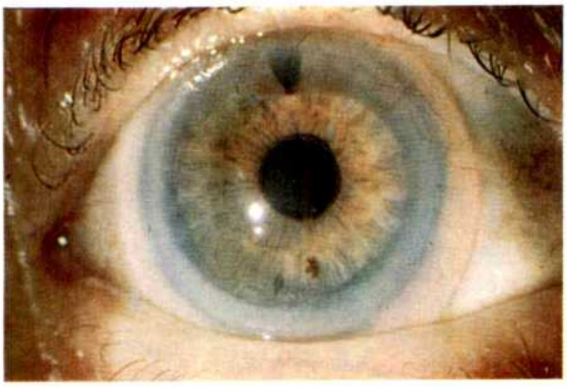

Fig. 1 (Kersley *et al.*) *Aphakic 'soft' contact lens worn continuously for six months achieving a visual acuity of 6/6 without overcorrection.*

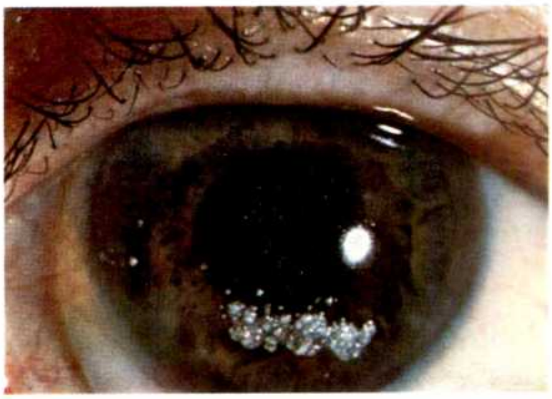

Fig. 2 (Kersley *et al.*) *Aphakic 'soft' contact lens for continuous wear showing the hard deposits that can develop.*

centre thickness. But other features play a part. The decreased water fraction in the tears of older people further complicates inadequate blinking. Certainly differential drying and temperature gradients across these thick lenses will encourage precipitation, and the fluctuating temperatures produced by lid and lens movement could produce deposition without any other help (Cordrey, 1976). Such precipitations will, of course, adhere to any surface irregularity or deformity (Tripathi and Ruben, 1976) and tear the surface apart (Fig. 3). These deposits have been estimated to contain calcium by autoanalysis of washings obtained from our contaminated lenses (Ganju and Cordrey, 1974; Ruben *et al.*, 1975). In the milky washings from some lenses a high reading was also found for chloride, but the significance of this is unknown.

Two solutions are available for use in removing deposits on Sauflon lenses where the corneal detergent action of methyl cellulose is ineffective. The first is a mixture of a copolymeric dispersant and sodium perberate as an oxidising agent, and it works satisfactorily on mucoprotein deposits, while the second contains the same dispersant but EDTA as the active agent for removing calcium-based deposits. The effectiveness of cleaning can be checked in a before-and-after method by ultraviolet spectography. As both these agents would be very dangerous in the eye, double heat treatment in saline is necessary before lenses are fit to be returned to the eye.

That the selection of patients must be considered very carefully for continuous wear is a factor that has become increasingly more important. It is the patient selection that will alter the statistics of ensuing problems and mark success versus failure from the patient's point of view. The question that has been asked, 'What do you do with the aphakic patient that has to be taken off continuous wear?' has to some extent answered itself. At six weeks patients are still relatively unused to their new vision, and careful consideration of their future and their existing circumstances may result in corneal contact lens fitting or even the prescription of aphakic spectacles. This can be carried out with relatively little disturbance to the patient at this early stage. The points to be considered are: (*a*) The patient's age: in younger patients a corneal contact lens would be favoured. (*b*) Their visual requirements; people neither going out a lot nor reading much would possibly be happy with a slightly reduced visual acuity and the absence of handling problems which the continuous wear lens affords. (*c*) Patients with physical handicaps; these are commoner in the aphakic group, and the patients would be better served by a continuous wear lens. (*d*) The in-

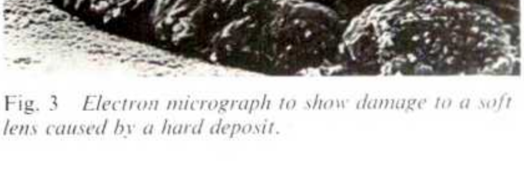

Fig. 3 *Electron micrograph to show damage to a soft lens caused by a hard deposit.*

ability of patients to co-operate and attend hospital again for regular check-ups or if problems occur is a factor that may argue against such a lens.

We acknowledge the generous participation of Contact Lenses Manufacturing Ltd in the supply of lenses and cleaning materials.

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Fluorescein angiography of the hereditary choroidal dystrophies

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SUMMARY The hereditary choroidal dystrophies are divided into (1) geographic choroidal dystrophies (central areolar, peripapillary, generalised), (2) gyrate atrophy, and (3) choroideremia. Each of these disorders is discussed with regard to mode of inheritance, age of onset, symptoms, fundus appearance, and visual function testing. A typical case history of each disorder is presented together with fluorescein angiography, and the fluorescein angiographic findings are related to our present understanding of these diseases.

Fluorescein angiography was found to be most helpful in diagnosing the early cases, by confirming the absence of the choriocapillaris, and in demonstrating either a local or general abnormality. The role of fluorescein angiography in understanding the aetiology of choroidal dystrophies is discussed.

The hereditary choroidal dystrophies can be classified in the following manner: (1) the geographical choroidal dystrophies, which can be further subdivided into (*a*) central aerolar choroidal dystrophy, (*b*) peripapillary choroidal dystrophy, and (*c*) generalised choroidal dystrophy; (2) gyrate atrophy; and (3) choroideremia. Each of these disorders has a particular mode of inheritance (Table 1). In the early and middle stages of each disease there is usually a characteristic fundus appearance, and this, together with the appropriate family history, is usually sufficient to make the correct diagnosis. However, in the earliest stages of these dystrophies the fundus change may not be as obvious. It is in these cases that fluorescein angiography provides a great deal of helpful information.

This paper describes the role of fluorescein angiography in diagnosing and in understanding the hereditary choroidal dystrophies.

Methods and materials

From a large group of patients with choroidal disease a group was selected which represented different aspects of the hereditary choroidal dystrophies. All patients were seen at the NYU-Bellevue Retinal Clinic and underwent complete ophthalmological examination.

All patients had fluorescein angiography, and certain psychophysical and electrophysiological diagnostic tests (Goldmann visual fields, electroretinography (ERG), electro-oculography (EOG), and retinal profiles) were performed where indicated. The procedures followed in this laboratory for such testing are fully outlined in previous papers (Carr *et al.*, 1966a; Carr *et al.*, 1966b).

Results

I. GEOGRAPHIC CHOROIDAL DYSTROPHY

This group of disorders is subdivided into three separate entities based on the geographical distribution. The areas which appear ophthalmoscopically normal are functionally normal as measured by psychophysical and electrophysiological testing.

A. *Central areolar choroidal dystrophy*

Central areolar choroidal dystrophy is inherited in an autosomal dominant manner (Sandvig, 1955;

Table 1 *Hereditary choroidal dystrophies*

- I. Geographic choroidal dystrophy
  - *A.* Central areolar choroidal dystrophy (autosomal dominant)
  - *B.* Peripapillary choroidal dystrophy (autosomal recessive)
  - *C.* Generalised choroidal dystrophy (autosomal dominant)
- II. Gyrate atrophy (autosomal recessive)
- III. Choroideremia (X-linked recessive)

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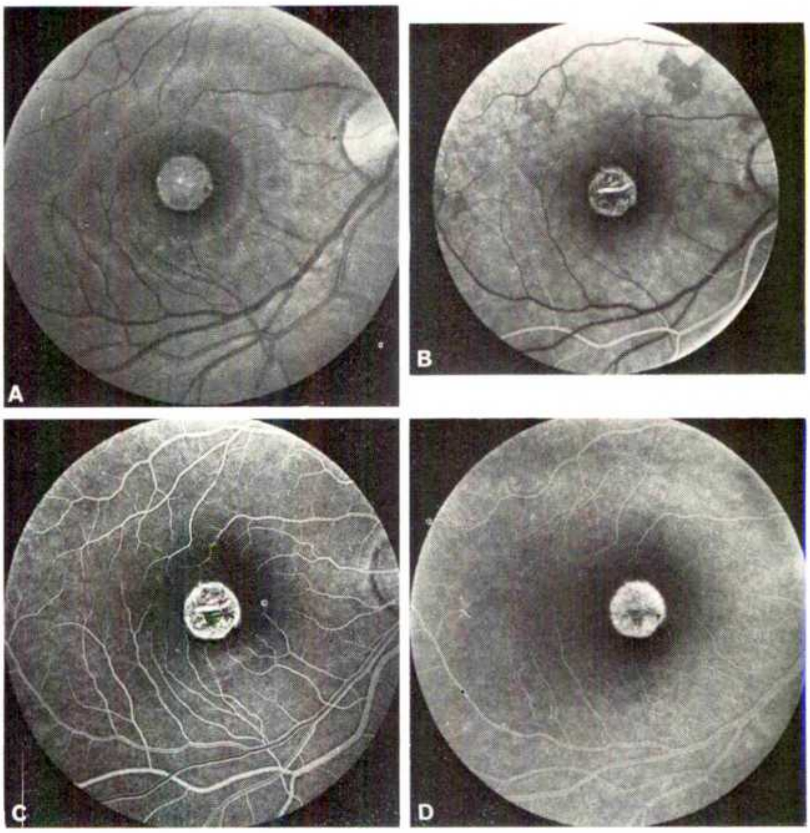

Fig. 1 (Noble, Carr, and Siegel) (case 1) CENTRAL AREOLAR CHOROIDAL DYSTROPHY. (A) *Well-circumscribed, circular macular lesion with a central tapetal 'sheen' surrounded by a heaping of pigment.* (B) *Arterial phase—large choroidal vessel traversing central macular lesion and surrounded by a few smaller choroidal vessels.* (C) *Mid venous phase; smaller choroidal vessels more easily seen.* (D) *Late phase; hyperfluorescence of the macula due to leakage from adjacent normal choriocapillaris*

Carr, 1965), though autosomal recessive cases (Waardenberg, 1952; Sorsby and Crick, 1953) have been occasionally reported. The onset is in the late second decade to the early fourth decade, with the initial symptom of diminished central visual acuity related to the macular location.

The lesion occupies the central macular area of each eye and is solitary, circumscribed, and circular or ovoid in shape. Although it may increase in size and become irregular in shape, it does not involve the peripapillary region or extend beyond the temporal vessel arcades.

The early fundus picture includes a mottling of the pigment epithelium or a tapetal 'sheen'. At this stage the underlying choroid may appear ophthalmoscopically normal, but with the subsequent loss of pigment epithelium the underlying choroidal vessels are more easily seen. They may be orange-red or yellowish-white in colour. With the continued loss of pigment and choroidal tissue the larger choroidal vessels are more easily seen. In the final stages the sclera is visible with the choroidal vessels coursing above.

Psychophysical and electrophysiological tests confirm that this is not a generalised disorder but is restricted to the area of the visible lesion. The peripheral visual fields are full and a central scotoma can be demonstrated. Dark-adapted final thresholds are elevated in the macular area but are normal beyond it. The electroretinogram is either normal or shows a diminished photopic response, and the EOG light rise is normal (Carr, 1965).

Case 1 (Fig. 1)

This 30-year-old male had a history of decreasing vision in both eyes of three years' duration. He denied any family history of similar eye disease but none of his family, all living in Pakistan, were examined. His parents are distant cousins.

The best corrected vision was 20/80 – OD and 20/40 + OS. Both fundi demonstrated a well-circumscribed, circular macular lesion which appeared as a central tapetal 'sheen' surrounded by a heaping of pigment. The remainder of the retina was completely normal.

Colour vision testing on the AOHRR plates was

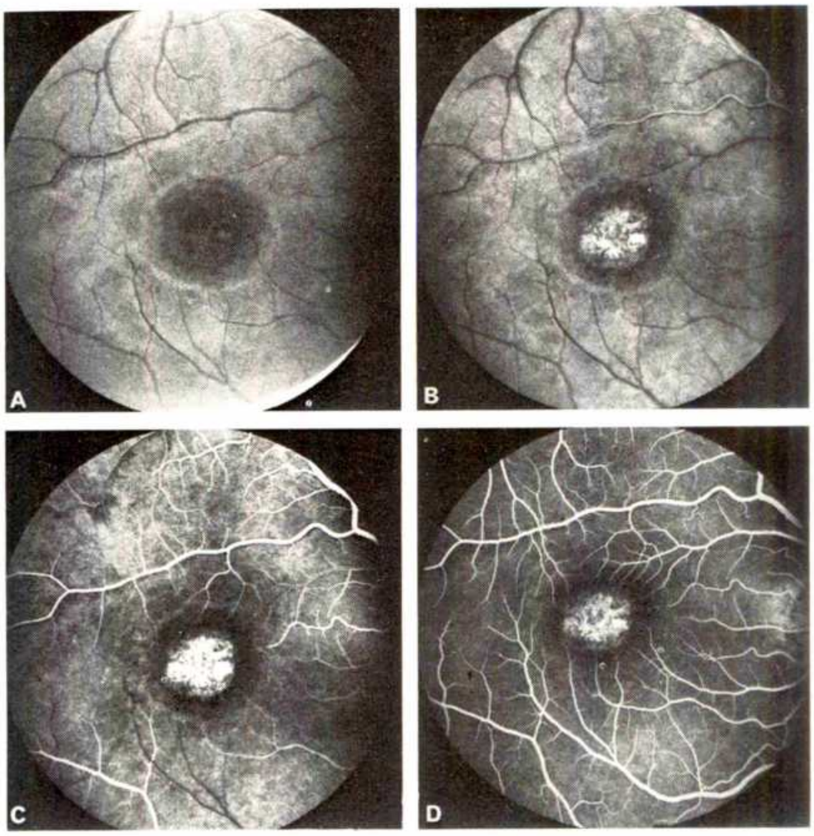

Fig. 2 (Noble, Carr, and Siegel) (case 2) JUVENILE HEREDITARY MACULAR DEGENERATION. (A) *Diffuse macular tapetal reflex.* (B) *Arterial phase; hyperfluorescence of macula due to underlying pigment defects. Choroidal vessels are not apparent.* (C) *Early venous phase; increase in the macular hyperfluorescence.* (D) *Late venous phase; no evidence of fluorescein dye leakage*

normal. Visual fields on the Goldmann perimeter (0·25 and 1 mm^2 white test objects at full illumination) revealed full peripheral fields and a small (3°) central scotoma in each eye. The electroretinogram and electro-oculographic light rise were normal.

On fluorescein angiography a large choroidal vessel was easily seen traversing the central macular lesion with a few smaller choroidal vessels surrounding it. The vessels filled initially in the choroidal phase and gradually became obscured as fluorescein from adjacent normal choriocapillaris leaked in at the border. The absence of choriocapillaris was confined to the macular lesion and the remainder of the choriocapillaris was normal.

This case represents an early stage of central areolar choroidal dystrophy which presented ophthalmoscopically as a well-circumscribed macular degeneration with a tapetal sheen. Although the choroid beneath the pigment disturbance appeared normal on fundus examination, fluorescein angiography clearly demonstrates the absence of the choriocapillaris.

Compare this fluorescein picture to what is seen in the early stages in another hereditary macular degeneration which may look similar on ophthalmoscopy.

Case 2 (Fig. 2)

This 18-year-old male had a two-year history of decreased vision in both eyes. He denied a family history of similar ocular disorders.

Visual acuity was 20/80 OD and 20/200 OS. The macula of each eye had mild changes in the pigment epithelium in an irregular fashion with the suggestion of a tapetal reflex. Peripheral visual fields were full and an electroretinogram was normal.

A fluorescein angiogram showed hyperfluorescence of dye in the macular region of each eye.

In this case fluorescein angiography revealed a hyperfluorescence of dye due to the increased transmission from the underlying normal choriocapillaris. The defect on fluorescein angiography in this case was only in the retinal pigment epithelium.

B. *Peripapillary choroidal dystrophy*

The peripapillary variant of choroidal dystrophy is

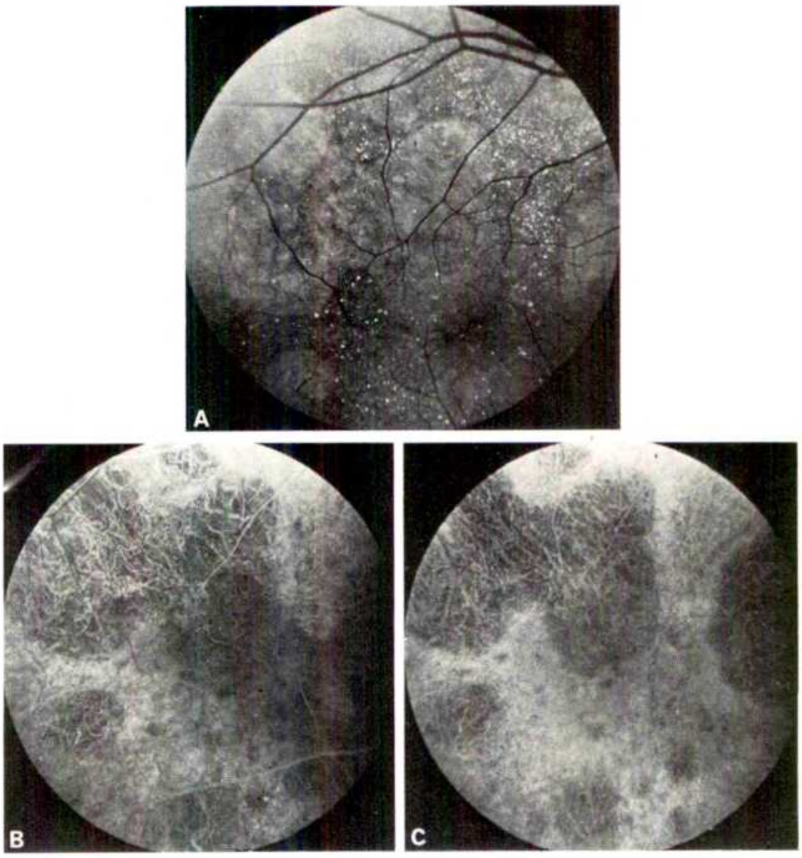

Fig. 3 (Noble, Carr, and Siegel) (case 3) PERIPAPILLARY CHOROIDAL DYSTROPHY. (A) *Multiple irregular areas of pigmentary loss. Tiny glistening yellowish-white spots are scattered throughout the posterior pole over normal appearing retina.* (B) *Mid venous phase; area of pigment loss shows an absent choriocapillaris with the larger choroidal vessels visible.* (C) *Late phase; the normal choriocapillaris flush emphasises the contrast with the abnormal choroid in which the large choroidal vessels remain visible*

inherited as an autosomal recessive (Svensson, 1939; Krill and Archer, 1971) but in many cases a positive family history is lacking. The onset is probably similar to the central areolar variety, although symptoms may occur later when the macula is affected and the vision reduced.

The development of the fundus picture is similar to central areolar choroidal dystrophy, with early changes seen in the retinal pigment epithelium and later an ophthalmoscopically apparent loss of pigment and choroidal tissue. The important distinction between these two disorders is their location. The peripapillary variety begins in the region surrounding the optic disc and slowly enlarges, in finger-like projections, nasally, along the temporal vessels, and into the macula, eventually occupying the entire posterior pole.

Visual fields and dark-adapted final thresholds indicate that peripheral to the involved area retinal function is normal. The electroretinogram is either normal or only slightly reduced, reflecting the extent of the disease (Krill and Archer, 1971; Carr *et al.*, 1975).

Case 3 (Fig. 3)

This 54-year-old male complained of decreased vision in the right eye of three weeks' duration. He denied a family history of any similar ocular disorder, though his parents may have been distant relatives. Family members were not available for examination.

The corrected vision was 20/30 OD and 20/20 – OS. Fundus examination showed multiple irregular areas of pigment epithelial loss in the posterior polar region in both eyes. Over these regions were scattered tiny glistening yellowish-white spots.

Final dark-adaptation thresholds were elevated 3 log units between 3 and 15° in the superior and temporal quadrants and between 3 and 25° in the nasal quadrant. More peripheral areas showed normal thresholds. An electroretinogram showed a slight reduction in the photopic and scotopic B-wave amplitude. The EOG light rise was normal.

Fluorescein angiography demonstrated the loss of the pigment epithelium, while beneath these affected regions the choriocapillaris was absent and the choroidal vessels were visible. Adjacent areas appeared completely normal.

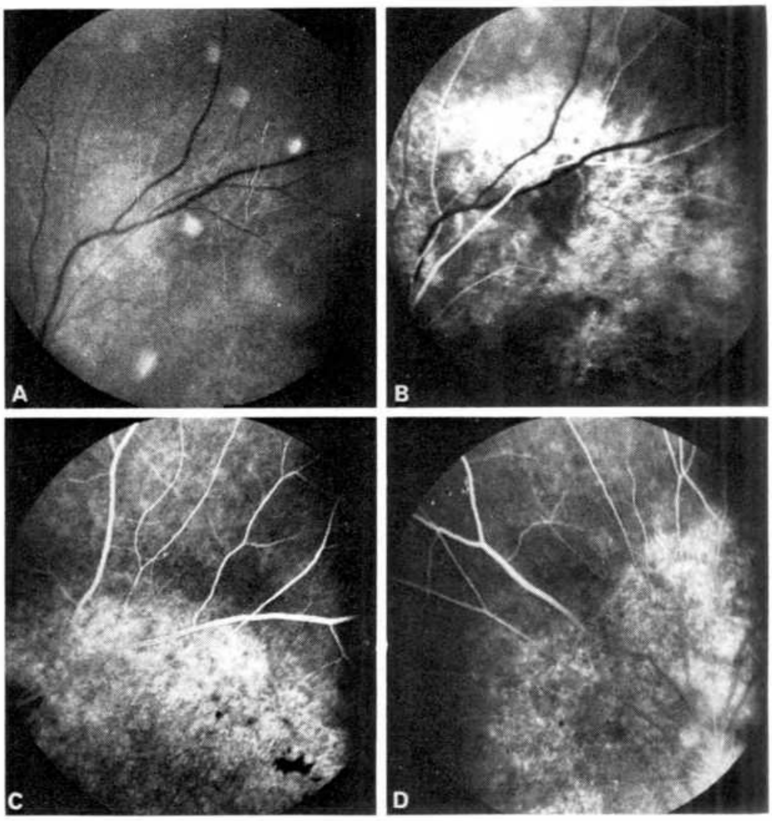

Fig. 4 (Noble, Carr, and Siegel) (case 4) PERIPAPILLARY PIGMENTARY DYSTROPHY. (A) *Superior temporal vessels of left eye demonstrating irregular ill-defined loss of pigment epithelium. White spots are artifacts.* (B) *Arterial phase; hyperfluorescence in affected area due to pigment epithelial loss.* (C) *Mid venous phase; hyperfluorescence persists and contrasts with normal fluorescein pattern superiorly. A few bone spicules are visible inferiorly.* (D) *Peripapillary area of the left eye indicating the distribution of the pigment changes*

Cases 4, 5, 6 (Fig. 4)

These three siblings, a female aged 53 (case 4), her sister, aged 62 (case 5), and the brother, 66 years old (case 6), gave a similar history of poor central vision since the middle of their third decade. The parents are first cousins and there is a history of consanguinity in both the maternal and paternal grandparents.

The vision in each eye of all three ranged from 10/400 to counting fingers at 1 ft. The posterior polar areas showed a generalised loss of the pigment epithelium with irregular borders separating the abnormal central retina from the normal-appearing periphery. Perivascular bone spicule pigmentation and several pigment strands were also seen within the affected regions.

The visual fields performed on cases 5 and 6 demonstrated large, dense central scotoma (64 mm^2 white test object) in each eye which corresponded to the fundus area involved. The peripheral fields were full or showed only a slight depression. The electroretinographic findings were variable—a slight reduction in the scotopic amplitude and a normal photopic response (case 4), a small photopic response without a scotopic increment (case 5), and an absent response (case 6).

Fluorescein angiography, performed in cases 4 and 5, showed a hyperfluorescence in the affected posterior polar region which was due to the retinal pigment epithelium loss, but there was no evidence of choriocapillaris loss. Peripheral areas adjacent to the dye hyperfluorescence were completely normal. Angiographic studies could not be performed in case 6.

The fundus appearance of peripapillary choroidal dystrophy, like central areolar choroidal dystrophy, need not always show obvious, well-defined areas of pigment loss revealing the underlying larger choroidal vessels. The appearance and geographic location of the lesion in case 3 is not dissimilar from that seen in cases 4, 5, and 6, and functional tests indicated a localisation to the peripapillary and macular area.

Comparison of the fluorescein angiogram, however, revealed significant differences. In case 3 the choriocapillaris and retinal pigment epithelium are absent and the larger choroidal vessels are seen throughout the sequence, whereas in cases 4, 5, and 6

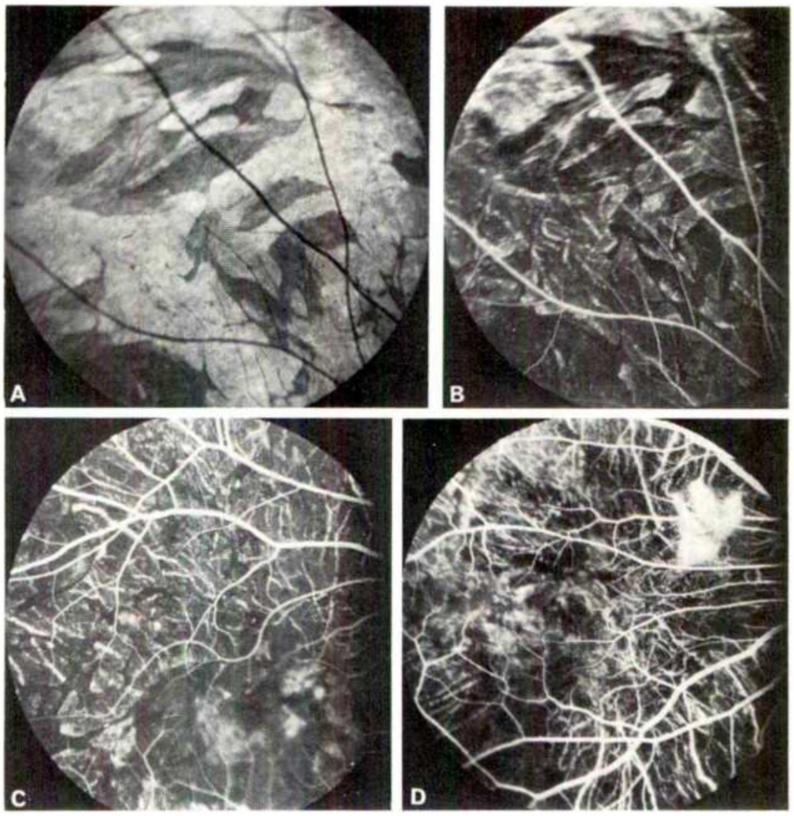

Fig. 5 (Noble, Carr, and Siegel) (cases 7 and 8) GENERALISED CHOROIDAL DYSTROPHY. (A) *Representative area of the fundus demonstrating a generalised loss of the pigment epithelium with scattered islands of irregularly shaped pigment accumulation.* (B) *Fluorescein angiography shows an absence of the choriocapillaris with the larger choroidal vessels demonstrating calibre irregularities. The islands of pigment accumulation result in hypofluorescence.* (C and D) *Fluorescein angiography of the macula of the right eye of cases 7 and 8 respectively demonstrating the profound generalised loss of the choriocapillaris. Gliotic changes are noted in the macula of Fig. C. The retinal vessels are normal*

the hyperfluorescence of dye is a result of changes in the retinal pigment epithelium only.

C. *Generalised choroidal dystrophy*

This diffuse disorder of the choriocapillaris is usually inherited as an autosomal dominant (Sorsby and Davey, 1955). The onset of symptoms is in the third and fourth decade and is usually manifested subjectively by diminished visual acuity. While symptoms of night blindness may also be present, the subjective changes associated with the photopic system usually predominate.

The early fundus changes include pigment mottling, hypopigmentation, and transparency of the retinal pigment epithelium. Later there is diffuse atrophy of the retinal pigment epithelium and the choroid appears 'sclerotic' with yellowish-white bands. Both the posterior pole and the periphery are involved in varying degrees. Even with diffuse involvement in the more advanced stages the retinal vessels usually remain normal (Franceschetti *et al.*, 1974). In the end stages it cannot be differentiated from other diffuse chorioretinal diseases.

The psychophysical and electrophysiological studies reflect this diffuse involvement. Visual fields reveal a concentric peripheral constriction and the electroretinogram is either subnormal (Franceschetti *et al.*, 1974) or absent (McKay and Spivey, 1962).

Fluorescein angiography performed by Curry and Schonberg (1969) showed a loss of choriocapillaris and visualisation of the choroidal vessels beneath the transparent pigment epithelium. A few scattered areas showed a choroidal flush pattern indicative of some remnants of choriocapillaris.

The following two cases represent an unusual variant of a generalised choroidal dystrophy and show how fluorescein angiography may help in the understanding of certain puzzling disorders which do not fit into our current classifications.

Cases 7 and 8 (Fig. 5)

Two brothers, aged 11 years (case 7) and 9 years (case 8) have had poor vision since birth. There is no family history of similar ocular disorders or of consanguinity. Two siblings, the parents, and a paternal aunt and uncle were examined and found to be normal. The visual acuity in the older brother was 5/200 OU and in the younger brother 5/200 OD and 20/200 OS. There was no nystagmus. The fundus appearance of each child was essentially the same. The discs were pink, without evidence of atrophy, and the retinal vessels were normal. Throughout the entire retina there was a loss or thinning of the pigment epithelium associated with irregular bands and clumps of jet black pigment. In some areas there was glial proliferation and chorioretinal atrophy in which the choroidal vessels appeared 'sclerotic'. Scattered throughout were irregularly-shaped islands of pigment epithelial thinning in which the choroid appeared unaffected. The fundus colour was dark greyish-green, unlike the pink colour of unaffected family members. An electroretinogram was not detectable in either child.

The fluorescein angiogram was similar in each case, showing a profound loss of choriocapillaris in the islands of retinal pigment thinning. The choroidal vessels did not fill evenly and showed multiple calibre irregularities. Interspersed between the islands of choriocapillaris loss there was hypofluorescence due to the irregular pigment changes.

The fundus showed a transition from the early thinning of the retinal pigment epithelium, in which the choroid appears normal, to the stages of chorioretinal atrophy, choroidal 'sclerosis', and gliosis. The fluorescein angiogram showed that beneath the transparent retinal pigment epithelium the choriocapillaris was absent and the abnormal choroidal vessels were easily visualised. These findings lend support to the diagnosis of a hereditary congenital generalised choroidal dystrophy.

2. GYRATE ATROPHY

Gyrate atrophy is a rare choroidal disease which is inherited as an autosomal recessive (Waardenberg, 1939), although dominant pedigrees have been reported (Franceschetti *et al.*, 1974). The onset of symptoms occurs in the second and third decades and consists of poor night vision and constricted peripheral vision.

The fundus abnormality begins in the midperiphery with a thinning and transparency of the retinal pigment epithelium in which the underlying choroid may appear normal or 'sclerotic'. These areas are typically scalloped in shape and begin as separate isolated areas which may merge to form a garland wreath. The borders have a darker appearance due to pigment accumulation which increases the contrast between the adjacent normal and abnormal tissue.

Progression of the disease leads to pigment clumping, retinal pigment epithelium and choriocapillaris atrophy, and eventual disappearance of the entire choroid exposing the white sclera. The optic nerve and retinal vessels may be normal or abnormal (Krill and Archer, 1971; Franceschetti *et al.*, 1974; Kurstjens, 1965; Duke-Elder, 1966). These changes begin in the midperiphery and slowly extend anteriorly and posteriorly. In the late stages an annular ring of choroidal atrophy may be seen from the periphery to the posterior pole, usually sparing the macula.

The functional tests vary considerably from case to case and seem to be related to the extent of involvement (Franceschetti *et al.*, 1974).

Case 9 (Fig. 6)

This 12-year-old female with progressive myopia complained of the recent onset of poor night vision and decreasing side vision. There was no significant family history with regard to ocular disorders.

The corrected vision was 20/40 OD and OS with a -9·50 sphere in each eye. In the equatorial regions of both eyes there was a loss of the retinal pigment epithelium in a scalloped fashion. The disc, macula, and retinal vessels were normal. The peripheral visual fields were constricted bilaterally to 30° (64 mm^2 white test object), and an electroretinogram was absent.

Follow-up examination 10 years later revealed an increase in night and peripheral vision symptoms. The best vision was 20/200 OD and 20/50 +OS.

There was slight progression of the equatorial scalloped areas centrally and peripherally, and the sclera was visible in scattered areas. Final dark-adaptation thresholds in the left eye showed an elevation of one log unit above the normal value throughout the horizontal meridian except in the temporal retina at 25 and 30°, where the elevation was 3 to 4 log units above the normal value.

Fluorescein angiography demonstrated the sharp demarcation between normal and abnormal tissue. In the involved scalloped portion the choriocapillaris was absent, while in the peripapillary and macular regions the choriocapillaris flush was seen. In the area separating these two there was a decrease in the transmission of dye due to heavy pigment accumulation.

The fluorescein study in this case is in accord with the functional findings. The scalloped areas of pigment epithelial thinning and loss reveal on fluorescein angiography a profound loss of the choriocapillaris, while adjacent areas without the pigment epithelial disturbances show a normal choriocapillaris flush phase.

3. CHOROIDEREMIA

Choroideremia is a generalised degeneration inherited as an X-linked recessive (McCulloch and McCulloch, 1948). The onset of symptoms usually occurs in the first and second decade with night

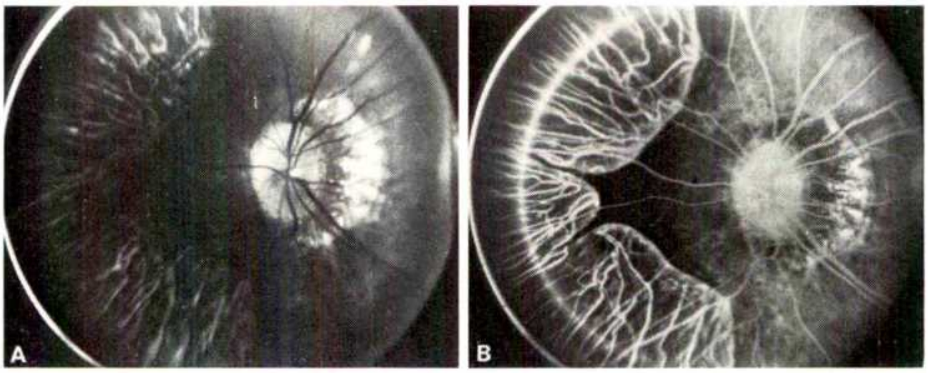

Fig. 6 (Noble, Carr, and Siegel) (case 9) GYRATE ATROPHY. (A) *Loss of pigment epithelium in a scalloped pattern revealing underlying white larger choroidal vessels. Peripapillary changes secondary to high myopia are present temporally.* (B) *Fluorescein angiography demonstrates the sharp demarcation between normal and abnormal tissue. The choriocapillaris is completely absent in the peripheral area while the choriocapillaris flush in other areas is normal. The border is highlighted by hypofluorescence due to pigment accumulation*

vision complaints. However, the actual lesion may begin earlier, because a 22-month-old infant with fundus changes has been described (McCulloch and McCulloch, 1948).

The fundus changes in the affected male undergo a typical progression. The initial appearance is a 'salt and pepper' pigment mottling in the equator and posterior pole. At this stage the electroretinogram is abnormal, showing a reduced or absent scotopic component, and final dark-adaptation thresholds are elevated (Franceschetti *et al.*, 1974).

Focal disturbances in the pigment epithelium consisting of pigmentary loss or a metallic sheen follow the 'salt and pepper' mottling and the underlying choroid may appear normal. Occasionally, these areas of focal disturbances assume a shape similar to gyrate atrophy, and the distinction between the two diseases may be difficult (Kurstjens, 1965). Atrophy of the choroid follows with eventual loss of the entire layer and exposure of bare sclera. The rate of progression will vary from individual to individual, and from family to family.

These changes begin in the mid-periphery and progress centrally, the macula being the last affected with central vision preserved until late in the disease. In the final stage the entire fundus shows the diffuse yellowish-white reflex of the sclera.

The carrier female usually has a picture similar to the earliest stage of the affected male (Goodman *et al.*, 1965). Typically there is pigment mottling, best seen in the mid-periphery.

Despite the similarity in appearance of carrier female and early affected males visual function tests (visual fields, final thresholds, electroretinogram) are usually normal in the female (Goodman *et al.*, 1965). In addition the fundus signs are stationary and visual function tests remain normal (Franceschetti *et al.*, 1974). There are occasional case reports in which the carrier female may have retinal and functional changes similar to the male, but such findings are a rarity (Fraser and Friedmann, 1968; Harris and Miller, 1968).

Case 10 (Fig. 7*a*, *b*) and Case 11 (Fig. 7*c*, *d*)

This 35-year-old female (case 10) and her 7-year-old son (case 11) were seen as part of a family study of choroideremia which was reported in an earlier paper (Goodman *et al.*, 1965). Neither patient had any visual symptoms, and the vision in each was 20/20 OD and OS.

The fundus examination of the mother showed the typical findings of a choroideremia female carrier—i.e., moderate pigment clumping scattered throughout the fundus. Visual fields, dark-adaptation curves, final thresholds, and the electroretinogram were normal.

Follow-up examination 13 years later revealed no interim complaints or fundus changes. Fluorescein angiography indicated a choriocapillaris flush which was altered by the overlying pigment abnormalities. Areas of pigment loss resulted in a transmitted hyperfluorescence, the fine pigment accumulation gave the choriocapillaris flush phase a 'stippled' appearance, and areas of heavy pigment accumulation led to hypofluorescence. There was no evidence of choriocapillaris atrophy.

The initial picture of the 7-year-old son (case 11) was remarkably similar to that of his mother with pigment clumping scattered throughout the fundus. Peripheral visual fields were mildly constricted (0·25

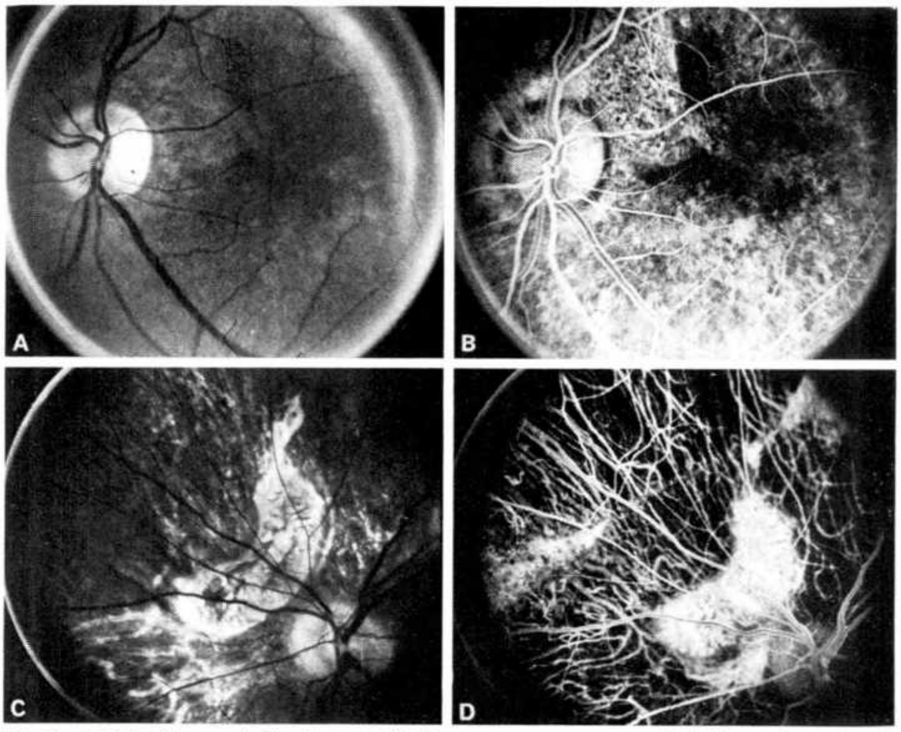

Fig. 7 (Noble, Carr, and Siegel) (case 10) CHOROIDEREMIA CARRIER. (A) *Disc and macula of left eye showing pigment mottling.* (B) *Fluorescein angiography shows a normal choroidal fluorescence altered by the fine pigment mottling. Superiorly larger areas of pigment accumulation result in hypofluorescence.* (Case 11) CHOROIDEREMIA. (C) *Superonasal to the disc in the left eye. Adjacent to the disc is an area of intraretinal neovascular gliosis. There is diffuse thinning of the pigment epithelium and the large choroidal vessels are seen as white cords. In the area between 9 and 11 o'clock the choroid appears normal.* (D) *Fluorescein angiography demonstrates a complete loss of choriocapillaris except for a small island. The 'normal appearing choroid is equally affected*

mm^2 white test object), final dark-adapted thresholds were elevated three log units, the amplitude of the photopic and scotopic electroretinogram response was reduced, and the electro-oculographic light rise was abnormal (130%).

Thirteen years later the visual acuity remained relatively stable at 20/40 OD and 20/20 OS but there was a subjective loss in side vision and night vision. At this time the fundus had a diffuse thinning of the retinal pigment epithelium, some areas showing loss with 'sclerotic' choroidal vessels, other areas appearing granular with a normal choroid. Isolated areas of glial proliferation were observed.

Fluorescein angiography revealed a loss of choriocapillaris throughout the entire fundus, in both the funduscopically normal and 'sclerotic' appearing choroid. The choroidal vessels were easily observed and showed no abnormality. Isolated areas including the macula revealed choriocapillaris present.

The fluorescein angiogram in this female carrier showed the choriocapillaris to be present throughout the fundus. The choriocapillaris flush phase was altered by the overlying pigment epithelial changes and appeared as a hyperfluorescence, a hypofluorescence, or as a fine stippling, the appearance depending on the nature of the change. Therefore, the only disturbance appreciated in the carrier female on fluorescein were the pigmentary abnormalities observed on fundus examination.

Krill (1969) noted that the carrier female and early affected males had a similar pigmentary mottling. Since fluorescein angiography of the carrier showed only an abnormality in the pigment epithelium, he reasoned that the primary defect was in the pigment epithelium. However, atrophy of the choriocapillaris that occurs early in choroideremia cannot always be easily visualised on fundus examination alone.

Thus, in the affected male (case 11) there were areas of the fundus which appeared similar to the female carrier—i.e., pigment mottling and normal choroid—but fluorescein angiography clearly showed complete choriocapillaris loss. Therefore, despite the similarities of the early affected male and the female carrier, the loss of choriocapillaris evident on fluorescein angiography may explain the difference in the visual function and prognosis of the disease.

Discussion

The hereditary choroidal dystrophies are a heterogeneous group of diseases in which an aetiology is not known. The common feature of these disorders is a loss of the choriocapillaris in the early stages which progresses to involve the retinal pigment epithelium, the photoreceptor layer, and in some cases the entire choroid. Whether the primary abnormality is in the choriocapillaris or in some other tissue has not been determined.

Certain of these dystrophies are generalised and progressive (choroideremia, generalised choroidal dystrophy) whereas others are localised, either remaining geographically confined (central areolar choroidal dystrophy) or progressively expanding (peripapillary choroidal dystrophy and gyrate atrophy) to involve more and more of the fundus.

The earliest ophthalmoscopic manifestations may range from subtle to marked alterations in the pigment epithelium. Mild pigment granularity, a tapetal 'sheen', pigment epithelial atrophy, or pigment accumulation may singly or in combination represent the first signs. These may be difficult to distinguish from certain other hereditary retinal degenerations or postinflammatory changes. Similarly in the end stages of the choroidal dystrophies the loss of retinal and choroidal tissue, exposure of the sclera, heavy pigment accumulation, and vascular changes cannot be easily differentiated from other degenerative and inflammatory conditions.

The role of fluorescein angiography in the study of the hereditary choroidal dystrophies is relatively new and seems to give useful information in diagnosing and understanding these disease entities. In terms of diagnosis the most helpful situation is in the early stages of the disease when the choroid appears normal and only the pigment epithelium is altered. In the hereditary choroidal dystrophies the absent choriocapillaris will be readily apparent on fluorescein angiography. During the choroidal flush phase the homogeneous dense background fluorescence due to choriocapillaris filling and subsequent leakage is absent and the large choroidal vessels remain visible throughout the entire sequence. When the pigment epithelium alone is involved without choriocapillaris disease, a normal choriocapillaris phase is seen though its appearance may be altered by the overlying pigment to show hyper- or hypofluorescence.

Fluorescein studies clearly distinguish between the generalised and local dystrophies. In central and peripapillary choroidal dystrophy as well as in gyrate atrophy there is a normal choriocapillaris flush adjacent to the involved tissue. In choroideremia and generalised choroidal dystrophy the choriocapillaris is involved throughout the retina, even though some areas may appear less involved than others.

With regard to an understanding of the aetiology, the role of fluorescein angiography is less obvious. Certainly the loss of the choriocapillaris is a very early sign, but so are the pigment abnormalities. A causal relationship has not been established. It is known, however, that in the early stages of many of the tapeto-retinal degenerations and certain hereditary macular degenerations (Best's, Stargardt's) fluorescein angiography does not indicate a choriocapillaris abnormality. This is one of the reasons such diseases are placed in the category of primary pigment epithelial-photoreceptor disorders. It is only in the very advanced stages that the choroidal vessels may be affected in these degenerations. By comparison, in the hereditary choroidal dystrophies the early loss of the choriocapillaris is seemingly of primary importance in the pathogenesis of these diseases.

In a discussion of these disorders it is important to clarify several facets of the problem. It would be virtually impossible to state with any degree of finality where the initial inciting abnormality begins. It is, however, difficult to imagine that there would be a situation in which there would be a choriocapillaris abnormality in which the dependent adjacent pigment epithelium was not involved. Yet there are many cases in which the converse can be seen—i.e., abnormalities of the pigment epithelium with a normal choriocapillaris. Thus, a hypothesis could be set forth denoting those diseases which in the early stages show an associated choriocapillaris abnormality and to theorise that this is the initial abnormality. Such cases would be under the broad umbrella of the choroidal dystrophies.

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Management of small elevated pigmented choroidal lesions

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SUMMARY The diagnosis of small choroidal melanomas may be difficult, and the natural history of these small tumours is poorly understood. We followed up 20 patients with the diagnosis of small choroidal melanomas for from 2 to 20 years. In 11 of these patients the melanoma was observed to grow. Nine of these patients have undergone enucleation. Eight of the eyes contained spindle B melanomas and one contained a melanoma of mixed cell type. None of the 20 patients has developed detectable metastatic disease. From this series and others reported it appears that close serial examinations without therapeutic intervention is safe in patients with small melanomas until growth is observed, and that there is little evidence to suggest that photocoagulation or radiotherapy is of greater benefit in those patients than close serial examination.

Controversy exists as to the correct management of small choroidal melanomas (Vogel, 1972; Westerfeld-Brandon and Zeeman, 1957; Stallard, 1968). The detection and clinical differentiation of pigmented choroidal lesions may present diagnostic difficulties (Ferry, 1964; Reese and Howard, 1967). Making the correct diagnosis is even more difficult in those patients with small choroidal masses and good visual acuities whom the clinician elects to follow closely without therapeutic intervention.

While there have been many clinical and pathologic studies of the natural history of choroidal melanomas most are not germane to the analysis of risk factors in patients with small tumours. Some of these studies were done before indirect ophthalmoscopy was in routine use (Morgan, 1973; Papolczy, 1937); some were done on relatively small numbers of patients (Jensen, 1963; Macrae, 1953); and some were done on specimens submitted by physicians with varying degrees of clinical acumen (Wilder and Paul, 1951; Paul *et al.*, 1962).

With the increased use of the indirect ophthalmoscopy and ancillary diagnostic tests our ability to diagnose smaller tumours has increased, but our understanding of the behaviour pattern of these smaller choroidal melanomas is still poorly delineated (Zimmerman, 1967; Shields and McDonald, 1974).

When a clinician observes a small, pigmented, choroidal mass he is faced with both a diagnostic and therapeutic dilemma. (1) is the lesion a choroidal melanoma? And (2) is it best treated by enucleation, photocoagulation, radiation, or observation alone? We have had the opportunity clinically to observe 20 patients with the diagnosis of small choroidal melanomas who have been followed up without therapeutic intervention for from two to 20 years. We think that the behaviour of their lesions may shed some light on the natural history and management of small pigmented choroidal mass lesions. The clinical course of these patients suggests that small asymptomatic melanomas can be safely followed without therapeutic intervention until definite growth is observed.

Methods

Twenty Caucasian patients with pigmented choroidal masses were seen in consultation. Most of the lesions were observed in visually asymptomatic patients on routine ophthalmological examinations. Sixteen of the 20 patients had initial visual acuities of 20/40 or better (Table 1). Thirteen patients were male and seven patients were female. All subjects had serial examination with direct and indirect ophthalmoscopy, fundus drawings, and Goldmann

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Table 1 *Patients with small choroidal melanomas*

Case No.	*Sex and eye*	*Age at onset*	*Length of follow-up*	*Ancillary diagnostic data*	*Initial visual acuity*	*Initial size—DD*	*Size at last examination*	*Length of follow-up since enucleation*
1	Male Left	39	19 years	Ultrasound, ^{32}P fluorescein	20/50	3× 3 DD	8× 5 DD	2 years
2	Male Right	41	20 years	Fluorescein	20/30	5 DD	5 DD	
3	Female Right	76	5 years	Fluorescein	20/25	4× 4 DD	7 DD	
4	Male Right	59	2 years	None	20/60	4× 4 DD	7× 4 DD	4 years
5	Female Right	61	3 years	Fluorescein, skin test, ^{32}P	20/20	3 DD	2 DD	
6	Female Left	47	8 years	Skin test Fluorescein	20/20	3× 4 DD	5 DD (Increased field defect)	2 years
7	Female Left	60	12 years	Skin test	20/20	3× 6 DD	5× 7 DD (Marked increased elevation)	
8	Female Right	65	2½ years	Fluorescein	20/50	4× 4 DD	5× 5 DD (Increased elevation and field loss)	6 years
9	Male Left	53	10 years		20/20	2·5× 3 DD	4× 4 DD	
10	Male Right	53	3½ years	Fluorescein	20/20	5× 5 DD	5× 5 DD	
11	Male Right	34	7 years	Fluorescein	20/40	3× 3 DD	3× 3 DD	
12	Male Left	60	10 years		20/20	4× 4 DD	6× 3 DD	
13	Male Right	63	13 years		20/20	2× 3 DD	Same (Increased elevation)	
14	Female Right	56	8 years		20/200	5× 5 DD	7× 7 DD (Increased elevation and field loss)	10 years
15	Male Left	42	4 years	Fluorescein	20/20	5× 5 DD (flat)	5× 5 DD (Increased elevation and field loss)	5 years
16	Male Right	29	6 years		20/20	3× 3 DD	15× 20 DD	5 years
17	Male Right	49	2 years		20/20	5× 5 DD	5× 5 DD (Markedly increased elevation and field loss)	8 years
18	Female Right	32	3½ years	Fluorescein, skin test, ultrasound, ^{32}P	20/20	4× 5 DD	4× 5 DD	
19	Male Right	51	3 years	Fluorescein, skin test, ultrasound	20/15	7× 7 DD	8× 8 DD (Markedly increased elevation)	
20	Female Right	51	12 years	Ultrasound (+) fluorescein (−) skin test	20/25	3× 4 DD	7 DD with marked elevation	2½ years

perimetry. Most patients had serial photographs taken, and some had ancillary diagnostic tests, including radioactive phosphorous uptake (3), ultrasound (4), fluorescein angiography (12), and a melanoma antigen skin test (6) (Table 1). None of these patients presented with a clinically apparent retinal detachment. Because of the patients' relatively good visual acuity, the small size of their lesions, and an intact Bruch's membrane, it was elected to follow them up after the possible malignant nature of their lesions was explained to them and all the therapeutic modalities were discussed. Patients were seen in follow-up at the University of California, San Francisco. In those cases where patients have left our geographical area, they and their current physicians have supplied follow-up information.

Results

All patients have been observed without therapeutic intervention for a period between two and 20 years (mean 7·8 years). On their initial examination the

Table 2 *Pathological data*

Case No.	*Cell type*	*Pigment*	*Break in Bruch's membrane*	*Retinal detachment*	*Vascularity*	*Intra-scleral invasion*	*Necrosis*	*Invasion to outer sclera*	*Intra-tumour*
1	Mixed-B	Light	(+)	(+)	Moderate	−	−	−	0
4	B	Light	(−)	(+)	Rare	−	−	−	−
6	B	Moderate	(−)	−	Rare	−	−	−	−
8	B	Light-moderate	−	−	Frequent	−	−	−	−
14	B	Light	−	−	Moderate	−	−	−	−
15	B	Moderate heavy	−	−	Moderate frequent	−	−	−	−
16	B*								
17	B	Light	−	+	Rare	−	−	−	−
20	B	Heavy	−	−	Frequent	−	−	−	−

*Pathology done at another institution, sections not available.

average size of the pigmented choroidal mass was 4 × 4 DD with 1 to 2 mm of elevation. All patients had large absolute field defects the same size or larger than their lesion.

During the period of observation 11 patients were noted to have an increase in the size of their choroidal mass or visual field defect. Two of these patients (cases 7 and 19) have refused any treatment despite the development of much larger tumours with the clinical appearance of collar button lesions. Two other patients (cases 15 and 17) had minimal attempts at photocoagulation prior to enucleation. A total of nine patients in this series have had enculations.

Patients who underwent enucleation were followed up for an average of 7·1 years prior to surgery (range 2 to 19 years) and for a mean of 4·9 years (range 2 to 10 years) after enucleation. To date no patient has developed metastatic disease. On histological examination (Table 2) 8 of 9 eyes were shown to contain spindle B melanomas, and one eye (case 1) had a mixed cell tumour. Only in the latter case were tumour cells noted at the outside edge of the sclera. In only one patient was intratumour necrosis and haemorrhage noted (case 8). Exudative retinal detachments were observed in eight eyes, and a break in Bruch's membrane was noted in four.

Nine patients were still being observed without therapeutic intervention. In six the pigmented choroidal masses appear to have remained stationary or to have shown relatively little visual field or fundoscopic change (mean follow-up 8·1 years, range 3·5 to 13 years). Three patients have had clinical courses suggestive of a spontaneous regression (cases 2, 5, 10), with a diminution of the size of their choroidal lesions and field defects, and with a change in the surrounding retinal pigment epithelium. None of these nine patients has developed any sign of metastatic disease on clinical or laboratory evaluations.

Ancillary diagnostic tests were done in 13 patients. Three have had radioactive phosphorous uptake tests. Case 1, which later underwent enucleation, had a positive test with over 100% uptake. Cases 5 and 18 had results between 20 and 90% uptake and are still being followed up. Four patients have had A and B scan ultrasonography. In three of these cases the results were consistent with the diagnosis of choroidal melanoma, and this was confirmed histologically. In case 18 significant elevation was noted without choroidal excavation, and the patient is still being followed up.

Immunological tests were done in six patients. All six patients had positive reactions with a soluble melanoma skin test antigen. To date the specificity and sensitivity of this test has been greater than 90% (Char *et al.*, 1974). Four of these patients have had the diagnosis of melanoma confirmed on pathological examination, one patient has refused enucleation despite a growing tumour, and another is being followed up. Twelve patients had fluorescein angiography. In five patients who were later enucleated three fluorescein angiograms were positive, two were equivocally positive, and one was negative. Of the seven patients who are still being followed up without therapeutic intervention two had characteristically positive angiograms and the other five had equivocal studies.

Discussion

Small pigmented choroidal lesions present the clinician with a diagnostic and therapeutic dilemma. Small choroidal melanomas, which most ocular oncologists define as less than 6 DD in diameter and 1 to 2 mm in elevation, can be difficult to diagnose. The presence of an absolute scotoma as large as the lesion has been one criterion which has been quite helpful in differentiating naevi from choroidal melanomas (Flindall and Drance, 1969; Naumann *et al.*, 1966; Naumann, 1970). While fluorescein angiography can be diagnostically useful when a characteristically positive pattern is observed, we and others have noted that it can often be falsely negative, especially in small melanomas (Pettit *et al.*, 1970; Hogeweg *et al.*, 1976). We have found that ultrasonography is an excellent diagnostic tool in the workup of patients with large melanomas. However, our experience with it in small melanomas is still too limited to ascertain its specificity and sensitivity. In our institution and in others some benign lesions have had some of the characteristic ultrasound findings of a melanoma (J. Shields, personal communication), and we have observed patients with a false positive ultrasound diagnosis of melanoma who on histological examination had a benign lesion.

The radioactive phosphorous uptake test is a useful aid in the diagnostic workup of patients with choroidal masses. However, as with the above tests, its sensitivity and specificity in small choroidal lesions are unclear. Patients with small melanomas may have negative ^{32}P tests and benign lesions may give false positive results (Hogeweg *et al.*, 1976; Cox, 1975). In patients whom we elect to follow up without therapeutic intervention we do not use the radioactive phosphorous test because of its established and theoretical risks. Ocular complications associated with the ^{32}P test include central retinal artery occlusion and intraocular haemorrhage (Burton, in press). At our institution we have observed these complications in less than 10% of ^{32}P studies done, but in patients who have good visual acuity whom we are planning to follow-up conservatively we feel this risk is unjustified. Further, we are concerned with the potential risks associated with this test. In some choroidal melanomas studied pathologically after ^{32}P testing the mechanical trauma of the ^{32}P probe appeared to increase the local dissemination of the tumour (unpublished observations). The dosage of ^{32}P given for diagnostic purposes (generally 500 to 750 μCi) is near the range of therapeutic ^{32}P dosage (2000 to 7000 μCi), and we have observed a number of patients who have had two and in one case three ^{32}P tests. The therapeutic use of ^{32}P has had significant morbidity associated with it (Modan and Lilienfeld, 1965; Lawrence *et al.*, 1969), and we do not feel it is justifiable to use this test unless we plan to enucleate an eye if a positive result is obtained.

In nine of the patients in this series histological confirmation of the diagnosis of small choroidal melanoma was made. In the 11 other patients (two of who have experienced marked tumour growth but have refused therapy) we think that our diagnosis of small choroidal melanoma is correct. All patients had pigmented choroidal lesions which had at least 1 to 2 mm of elevation, and had absolute visual field defects greater than the size of their lesions. These findings and the results of the ancillary tests support our diagnosis. However, as mentioned previously, some simulating lesions cannot be ruled out (Shields and Font, 1972; Howard and Forrest, 1967). To date, the incidence of pathologically documented false positive diagnoses of choroidal melanoma is less than 2% at our institution (unpublished observation). The incidence of false negative diagnosis is difficult to ascertain. We are unaware of any patient we have clinically examined and recommended for further observation developing a metastatic melanoma.

In a pathological study by Davidorf and Lang (1974) it was noted that less than 30% of the patients with small choroidal melanomas had died by the end of 10 years. Two other clinical studies also suggest a much better prognosis for the small choroidal melanoma than has generally been assumed. Curtin and Cavender (1974) reported on 14 patients with small melanomas who are being initially followed up without therapeutic intervention. Of this group of patients, followed up on the average for more than six years, 13 are reported to be alive and without metastatic disease. Rubinstein and Myska (1974) followed up 18 patients for 3 to 14 years and treated 13 of them with either photocoagulation, radiation, or enucleation. After that length of follow-up it was noted that all 18 were clinically alive and well. In our study none of the patients had developed metastatic disease. These results suggest that the morbidity for patients having small choroidal melanomas is under 25% at five years. It also would appear that patients with small choroidal tumours may be followed up for relatively long periods of time until growth is documented without morbidity. Our results agree with the observation by Flocks *et al.* (1955), Zimmerman (1967), and Shields and McDonald (1974) that small choroidal melanomas are predominantly spindle cell in type.

In numbers sufficient for evaluation the modalities of radiotherapy and photocoagulation have been used as an alternative to enucleation in patients with small choroidal melanomas. In a group of 100 patients treated with a ^{60}Co plaques Stallard (1966) noted that 69 were successfully treated with radiotherapy. Six patients died of metastatic disease, and in 25 cases the possibility of therapeutic failure or uncertainty about the progression of the tumour dictated enucleation. Using a slightly different method of irradiation, Lommatzsch (1974) irradiated 62 patients with ^{106}Ru/^{106}Rh beta applicators between 1964 and 1971. Of these patients 74% were considered to have undergone successful radiation; however, 26% had to have enucleation because of tumour growth or sequelae from the radiation. Some investigators have noted that radiotherapy to eye tumours has a significant incidence of morbidity

(MacFaul and Bedford, 1970). Meyer-Schwickerath and Vogel (1974) have treated 54 patients, most of whom had small choroidal melanomas, with photocoagulation, and followed them up for over 10 years. In this group 46% were thought to be successfully treated and 27% died with metastatic disease. Similar results with photocoagulation have been noted by Francois (1974).

Two important conclusions can be drawn from the data presented. First, small choroidal melanomas are generally of a more benign histological character and have an excellent five-year prognosis. Secondly, to date there is little evidence to suggest that in patients with small choroidal melanomas treatment with either photocoagulation or radiotherapy is of any benefit over close serial follow-up without therapeutic intervention. Such treatment may in fact be deleterious. It would also appear that patients with small choroidal melanomas that have not shown growth can be safely followed up for relatively long periods of time without increasing the risk of morbidity or mortality.

When patients have asymptomatic small pigmented choroidal lesions diagnosed as melanomas we inform them that he or she has a possible malignant tumour and explain the various therapeutic options. If the patient elects it, we believe that frequent serial examination without therapeutic intervention is a reasonable course of management in these cases. In such cases noninvasive diagnostic tests, especially ultrasonography, may prove to be very useful. We have not found fluorescein angiography very helpful in patients with small lesions, and we feel that in patients who are going to be followed up without the possibility of surgical intervention the ^{32}P test is contraindicated. In those patients whose tumour shows growth on serial examination further diagnostic studies, including ^{32}P tests, are done and enucleation is usually recommended. In patients who present to our institution with large choroidal melanomas, with poor visual acuity, and a secondary detachment, enucleation is routinely performed after thorough ocular and metastatic diagnostic examinations. If patients refuse enucleation, or have a melanoma in their only functional eye (one-eyed patients or those who are amblyopic in the non-involved eye) we believe that therapeutic modalities such as photocoagulation, radiotherapy, and possibly total eye wall resection present reasonable alternative modes of therapy (Peyman, 1974).

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HLA antigens and antinuclear antibody titres in juvenile chronic iridocyclitis

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SUMMARY HLA antigen frequencies and antinuclear antibody titres were studied in 43 patients with juvenile chronic iridocyclitis. We did not detect an increased incidence of HLA-B27 in patients having chronic iridocyclitis associated with juvenile rheumatoid arthritis or in patients with 'chronic iridocyclitis in young girls'. Both groups of patients had a statistically significant increased incidence of antinuclear antibodies. However, these antibodies were detected more frequently in patients with chronic iridocyclitis associated with JRA than in patients with 'chronic iridocyclitis in young girls'.

Approximately 15% of children with juvenile rheumatoid arthritis (JRA) develop chronic iridocyclitis (Chylack *et al.*, 1975). Most of the patients with ocular involvement are female and have the pauciarticular form of JRA (Key and Kimura, 1975). Similar ocular findings are observed in the syndrome known as 'chronic iridocyclitis in young girls'. However, these patients do not have inflammatory joint disease or any other identifiable illness (Perkins, 1966). Some investigators have observed a significantly increased prevalence of HLA-B27 and elevated antinuclear antibody titres among patients with juvenile rheumatoid arthritis (Rachelefsky *et al.*, 1974; Schaller *et al.*, 1974; Buc *et al.*, 1974; Edmonds *et al.*, 1974; Rahi *et al.*, 1976). We have studied a group of young patients with chronic iridocyclitis to determine whether a specific HLA antigen pattern or an elevation of the titre of antinuclear antibody was of diagnostic or prognostic importance in this disease entity.

Methods

Twenty-three patients with chronic iridocyclitis associated with juvenile arthritis were examined in the Uveitis Survey Clinic of the University of California, San Francisco, in 1976. Three were males, 20 were females, and all the patients fulfilled the criteria for the diagnosis of JRA as set forth by the American Rheumatism Association (Brewer *et al.*, 1973). The uveitis developed in all patients before the age of 16. Ten per cent of these patients initially presented to our clinic with the diagnosis of chronic anterior uveitis, and only on extensive physical and laboratory examination was the underlying juvenile rheumatoid arthritis diagnosed. Twenty-two of the 23 patients tested had either the monoarticular or pauciarticular form of JRA, and none of the patients had acute systemic illness.

Twenty female patients were examined in 1976 with the diagnosis of 'chronic iridocyclitis in young girls'. The mean age of these patients was 13·5 years, and the mean duration of their disease was 4·7 years. As in those patients with chronic iridocyclitis associated with JRA these patients manifested a low-grade bilateral chronic iridocyclitis with posterior synechiae, calcific band keratopathy, secondary cataract, and glaucoma. However, none of these patients has associated joint disease or other signs of systemic disease.

Seventy-two healthy individuals were also tested as control subjects. Most of these were personnel of the Department of Ophthalmology and of the Francis I. Proctor Foundation.

HLA typing was performed on peripheral blood lymphocytes isolated by the method of Böyum (1968), and microlymphocyte cytotoxicity tests were performed using the two-stage method of Amos (1974). More than 80 highly selected antisera were used to

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determine HLA antigens: A1, A2, A3, A9, A10, A11, A28, A29, AW30, and AW32 at the HLA-A locus; and the HLA-B antigens 5, 7, 8, 12, 13, 14, 18, 27, BW15, BW16, BW17, BW22, BW35, and BW40 were also tested.

Antinuclear antibody titres were tested using a standard indirect immunofluorescence technique at a dilution of 1 : 10. Blood samples positive for ANA were titred at dilutions of 1 : 16, 1 : 64, 1 : 256, 1 : 512, and 1 : 1024.

Statistical analysis was done by the chi-square test for the ANA data and the chi-square test with Yates's correction for the HLA data.

Results

The HLA antigen frequencies in the patient groups and in the control subjects are presented in Table 1. In the chronic iridocyclitis associated with JRA, HLA-A1, and A9 were slightly decreased, and A2 was slightly increased in the patients, as compared with the controls; however, these differences were not statistically significant. The HLA-B27 antigen was observed in 25% of patients having the syndrome of 'chronic iridocyclitis in young girls', in 27·7% of patients with chronic iridocyclitis associated with JRA, and in 6·9% of normal controls. These differences were also not statistically significant.

Table 2 shows the results of ANA titre determinations. Fifteen of 21 patients with chronic iridocyclitis associated with JRA (71·4%) were noted to have positive ANA tests. Six of 19 patients with the syndrome of 'chronic iridocyclitis in young girls' had positive ANA titres (31·6%) versus 0 out of 20 normal controls. Thus, both of the patient populations with chronic iridocyclitis had a statistically increased incidence of ANA antibody titres versus the normal control population in $P < 0·0001$ and $P < 0·02$, respectively. Patients with chronic iridocyclitis associated with JRA had a statistically significant increased incidence positive of ANA titres versus those patients with the syndrome of 'chronic iridocyclitis in young girls' ($\chi^2 = 4·8$, $P < 0·03$). There did not appear to be any correlation between HLA-B27 and ANA titres.

Table 1 *Frequency of HLA antigens in juvenile chronic iridocyclitis*

HLA antigen	*Controls (N = 72)*		*Chronic iridocyclitis associated with JRA (N = 23)*		*Chronic iridocyclitis in young girls (N = 20)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
HLA—A1	20	(27·8)	4	(17·4)	4	(20·0)
HLA—A2	34	(47·2)	16	(69·6)	10	(50·0)
HLA—A3	16	(22·2)	5	(21·7)	4	(20·0)
HLA—A9	18	(25·0)	4	(17·4)	6	(30·0)
HLA—A10	9	(12·5)	2	(8·7)	1	(5·0)
HLA—A11	10	(13·9)	3	(13·0)	3	(15·0)
HLA—A28	4	(5·6)	0	(0)	1	(5·0)
HLA—A29	5	(6·9)	1	(4·3)	0	(0)
HLA—AW30	5	(6·9)	0	(0)	1	(5·0)
HLA—AW32	7	(9·7)	2	(8·7)	2	(10·0)
HLA—B5	6	(8·3)	2	(8·7)	3	(15·0)
HLA—B7	18	(25·0)	4	(17·4)	5	(25·0)
HLA—B8	17	(23·6)	4	(17·4)	4	(20·0)
HLA—B12	19	(26·4)	7	(30·4)	4	(20·0)
HLA—B13	3	(4·2)	0	(0)	1	(5·0)
HLA—B14	7	(9·7)	2	(8·7)	3	(15·0)
HLA—B18	4	(5·6)	2	(8·7)	3	(15·0)
HLA—B27	5	(6·9)	5	(21·7)	5	(25·0)
HLA—BW15	7	(9·7)	3	(13·0)	1	(5·0)
HLA—BW16	3	(4·2)	0	(0)	0	(0)
HLA—BW17	6	(8·3)	1	(4·3)	1	(5·0)
HLA—BW22	3	(4.2)	0	(0)	1	(5·0)
HLA—BW35	8	(11·1)	1	(4·3)	3	(15·0)
HLA—BW40	10	(13·9)	3	(13·0)	2	(10·0)

Table 2 *IgG antinuclear antibodies*

Group	*Positive tests*	*%*
Chronic iridocyclitis associated with JRA	15/21	71·4*,‡
'Chronic iridocyclitis in young girls'	6/19	31·6†
Normal controls	0/20	0

*$\chi^2 = 19·55$, $P < 0·0001$ (difference between patients with chronic iridocyclitis associated with JRA and normals).
†$\chi^2 = 5·24$, $P < 0·02$ (difference between patients with 'chronic iridocyclitis in young girls' and normals).
‡$\chi^2 = 4·85$, $P < 0·03$ (difference between patients with chronic iridocyclitis associated with JRA and patients with 'chronic iridocyclitis in young girls').

Discussion

The HLA-B27 antigen was not significantly increased in patients with juvenile chronic iridocyclitis versus control subjects. Rachelefsky *et al.* (1974) noted that 42% of 26 patients with JRA had the B27 antigen. Buc *et al.* (1974) also observed an association between B27 and patients with JRA (29% of 34 patients). In this latter report the B27 antigen was present almost exclusively in those JRA patients with the polyarticular form of the disease. Edmonds *et al.* (1974) studied a group of patients with juvenile chronic polyarthritis. They noted that 14 out of the 15 JRA patients who eventually developed ankylosing spondylitis or sacroiliitis had HLA-B27. However, only 4 out of 20 JRA patients without sacroiliitis had this HLA phenotype. As we have observed in this study, previous reports by Nissilä *et al.* (1975) and Gibson *et al.* (1975) have also failed to note an association between the B27 antigen and patients with JRA. It is possible that the association between B27 and JRA observed by Rachelefsky *et al.* (1974) and Buc *et al.* (1974) could be due to an inclusion in their JRA patient population of some patients with juvenile onset ankylosing spondylitis. We think this is unlikely in our study for three reasons: (1) all of our patients with chronic iridocyclitis associated with JRA had the pauciarticular form of the disease, and it is probable that some of Buc *et al.'s* (1974) patients with polyarticular involvement may have had juvenile onset ankylosing spondylitis. (2) All of the patients in our study had a chronic low-grade iridocyclitis, whereas patients with ankylosing spondylitis of juvenile onset generally have an acute recurrent iridocyclitis. (3) Nearly 90% of our patients were females, whereas most of the patients affected by ankylosing spondylitis are males.

In our study it does not appear that the HLA-B27 antigen is associated with the chronic iridocyclitis of JRA or with the syndrome of 'chronic iridocyclitis in young girls'. It may, however, be a genetic marker for iridocyclitis associated with juvenile onset ankylosing spondylitis or sacroiliitis. We have noted that in adult patients with iridocyclitis that is associated either with or without ankylosing spondylitis, there appears to be an increased frequency of B27 (unpublished data).

In our current study the incidence of positive ANA titres was significantly increased in juvenile chronic iridocyclitis. Patients carrying the diagnosis of chronic iridocyclitis associated with JRA showed a significantly higher prevalence of positive ANA results than patients with the syndrome of 'chronic iridocyclitis in young girls'. Ninety per cent of patients with the uveitis associated with JRA develop their arthritis first; however, 10% showed the onset of iridocyclitis with the development of systemic signs of JRA. The average length of follow-up in the patients with the syndrome of chronic iridocyclitis in young girls was 4·7 years, so we think that the likelihood of these patients developing JRA is probably small. However, even in Perkins's (1966) initial description of this syndrome it was noted that a few patients developed arthritis later on. Schaller *et al.* (1974) reported that 30% of patients with JRA without uveitis had positive ANA tests. The role of ANA in the development of the uveitis and of the arthritis remains obscure. In our study there was a significantly higher prevalence of positive tests for ANA among patients with JRA than among patients with 'chronic iridocyclitis in young girls'. It is possible that the risk of developing JRA among the patients with the syndrome of 'chronic iridocyclitis in young girls' may be predicted by the presence of a positive ANA test. An alternative suggestion is that positive tests for ANA may be helpful in predicting which patients with juvenile rheumatoid arthritis will develop chronic iridocyclitis.

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HLA antigens and uveitis

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SUMMARY We have studied the antigen frequencies in a group of adult patients with acute and chronic iridocyclitis and chronic cyclitis. In patients with iridocyclitis a statistically significant increased incidence of HLA-B27 was noted, even in those patients without joint or systemic disease. Patients with chronic iridocyclitis also were noted to have an increased incidence of B27; however, those patients with chronic cyclitis did not. On the basis of HLA-B27 studies there appears to be a fundamental difference between adult and juvenile iridocyclitis.

A number of investigators have noted an association between HLA-B27 and acute anterior uveitis (Brewerton *et al.*, 1973; Ehlers *et al.*, 1974; Mapstone and Woodrow, 1974; Brewerton and James, 1975; Woodrow *et al.*, 1975). Both ankylosing spondylitis and Reiter's syndrome are associated with iridocyclitis, and there is a statistically significant increased incidence of HLA-B27 in these systemic diseases (Caffrey and James, 1973; Brewerton *et al.*, 1973; Schlosstein *et al.*, 1973; Aho *et al.*, 1973; Zachariae *et al.*, 1973; Woodrow, 1973). We have studied the HLA antigen frequencies in a group of adult patients with acute and chronic iridocyclitis and with chronic cyclitis to determine whether factors such as the chronicity of inflammation, the presence of associated joint or systemic disease, or the sex of the patient are specifically related to certain HLA antigen frequencies.

Materials and methods

Fifty-three unrelated patients with uveitis were typed for HLA antigens. Thirty-nine had iridocylitis of adult onset. Nineteen of these were males and 20 were females with an age range from 25 to 68 years (mean 42·6 years). Twenty of these patients had acute recurrent iridocyclitis and had characteristic symptoms at the onset of each episode including: ocular pain, conjunctival injection, photophobia, epiphora, and blurred vision. Nineteen patients had chronic iridocyclitis, although eight had initially presented with an acute episode. Patients with chronic iridocyclitis had a painless anterior uveitis of greater than six months duration which was poorly responsive to medication. Seven male and seven female Caucasian patients were thought to have chronic cyclitis; their ages ranged from 5 to 67 years (mean 26·6 years). All of these patients had an acute onset of uveitis, the most frequent chief complaint being floating spots. On ophthalmological examination patients with chronic cyclitis showed cellular opacities in the anterior vitreous, large vitreous snowballs, and 'snow banking' on the inferior pars plana.

All patients were examined by at least two examiners. The cases were classified as iridocyclitis when the inflammation was predominantly in the anterior chamber of the eye; and the diagnosis of chronic cyclitis was made by the clinical findings described above.

HLA typing was performed by the microlymphocyte cytotoxicity test for 10 HLA-A and 14 HLA-B specificities described previously (Ohno *et al.*, submitted for publication). The frequency of HLA antigens in patients with acute and chronic iridocyclitis and with chronic cyclitis of adult onset was compared with 72 normal control subjects using a chi-square test with Yates's correction.

Results

The distribution of HLA antigens among 33 Caucasian patients with acute and chronic iridocyclitis of adult onset and among normal adult control subjects is presented in Table 1. There were no statistically significant alterations in the HLA-A locus antigen frequencies in the patient versus the

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control populations. Eighteen out of 33 patients (54·5%) were positive for HLA-B27, in contrast to 5 out of 72 (6·9%) normal controls ($\chi^2 = 27{\cdot}3$, $P < 0{\cdot}0001$). The frequency of HLA-B27 was analysed according to the presence or absence of associated joint disease, systemic disease, and sex (Table 2). Eleven of 19 males (57·9%) were positive for HLA-B27 as were nine of 20 females (45%). In the category of ankylosing spondylitis five out of seven patients were B27 positive. Two patients with Reiter's disease, one patient with sacroiliitis, and one patient with osteitis condensans ilii were also noted to have the HLA-B27 antigen. Among 26 patients with iridocyclitis (9 males and 17 females) there were no physical or roentgenologic signs of either joint or systemic disease. Eleven of these patients (42%) also were B27 positive.

The frequency of HLA-B27 was also analysed according to the chronicity of the iridocyclitis. In acute recurrent iridocyclitis 12 out of 20 patients (60%) were positive for HLA-B27. Among patients with chronic iridocyclitis eight out of 19 (42%) were positive; this difference was not statistically significant. There was no difference in the HLA-B27 frequency between patients with unilateral versus bilateral iridocyclitis, and we did not note any significant correlations between the severity of the iridocyclitis and HLA-B27.

Discussion

Acute and chronic iridocyclitis of adult onset has a highly significant association with the HLA-B27 antigen in contrast to juvenile chronic iridocyclitis and chronic cyclitis (Ohno *et al.*, 1977). Brewerton *et al.* (1973) first reported the association of acute anterior uveitis and HLA-B27. They noted that 55% of 44 patients with acute anterior uveitis had HLA-B27. Twenty-nine per cent of 24 patients with acute anterior uveitis without systemic disease were also positive for B27. These findings have been confirmed in the case of acute recurrent uveitis, but not in chronic uveitis, by Ehlers *et al.* (1974). Mapstone and Woodrow (1974) studied 59 patients with acute anterior uveitis and 32 (54%) had the HLA-B27 antigen. Among 41 patients without systemic disease 17 (42%) were also positive. Similar B27 frequencies were recently reported by Brewerton and James (1975) and Woodrow *et al.* (1975).

Iridocyclitis associated with ankylosing spondylitis and with Reiter's disease has a close association with HLA-B27, because the systemic disease itself has a significant correlation with HLA-B27. Sacroiliitis seems to be one of the most important forms of arthritis associated with iridocyclitis. In both ulcerative colitis and in Reiter's disease uveitis was found more often in patients with sacroiliitis than those without it (Wright *et al.*, 1965; Oates and Young, 1959). In our series, 42·3% of the 26 patients who had no sacroiliitis or associated systemic disease had the HLA-B27 ($\chi^2 = 15{\cdot}0$, $P < 0{\cdot}0001$). There was no difference in the percentage of males or females having uveitis without systemic disease.

It is possible that patients with iridocyclitis and HLA-B27 may have subclinical or asymptomatic sacroiliitis, and we suspect these patients may represent an incomplete form of the uveitis syndrome associated with ankylosing spondylitis or Reiter's disease.

Ehlers *et al.* (1974) did not find an increased incidence of HLA-B27 in chronic uveitis. In our

Table 1 *Frequency of HLA antigens in adult iridocyclitis and chronic cyclitis*

HLA antigen	*Controls (N = 14)*		*Adult iridocyclitis (N = 33)*		*Chronic cyclitis (N = 11)*	
	No.	*%*	*No.*	*%*	*No.*	*%*
HLA—A1	20	(27·8)	6	(18·2)	6	(42·9)
HLA—A2	34	(47·2)	19	(57·6)	3	(21·4)
HLA—A3	16	(22·2)	7	(21·2)	4	(28·6)
HLA—A9	18	(25·0)	5	(15·2)	3	(21·4)
HLA—A10	9	(12·5)	4	(12·1)	4	(28·6)
HLA—A11	10	(13·9)	4	(12·1)	1	(7·1)
HLA—A28	4	(5·6)	2	(6·1)	1	(7·1)
HLA—A29	5	(6·9)	2	(6·1)	0	(0)
HLA—AW30	5	(6·9)	2	(6·1)	0	(0)
HLA—AW32	7	(9·7)	4	(12·1)	1	(7·1)
HLA—B5	6	(8·3)	2	(6·1)	1	(7·1)
HLA—B7	18	(25·0)	8	(24·2)	4	(28·6)
HLA—B8	17	(23·6)	5	(15·2)	4	(28·6)
HLA—B12	19	(26·4)	7	(21·2)	3	(21·4)
HLA—B13	3	(4·2)	1	(3·0)	1	(7·1)
HLA—B14	7	(9·7)	2	(6·1)	1	(7·1)
HLA—B18	4	(5·6)	3	(9·1)	2	(14·3)
HLA—B27	5	(6·9)	18	(54·5)*	0	(0)
HLA—BW15	7	(9·7)	4	(12·1)	1	(7·1)
HLA—BW16	3	(4·2)	1	(3·0)	1	(7·1)
HLA—BW17	6	(8·3)	1	(3·0)	1	(7·1)
HLA—BW22	3	(4·2)	0	(0)	0	(0)
HLA—BW35	8	(11·1)	5	(15·2)	1	(7·1)
HLA—BW40	10	(13·9)	4	(12·1)	2	(14·3)

*$\chi^2 = 27{\cdot}3$, $P < 0{\cdot}0001$.

Table 2 *Frequency of HLA-B27 and associated diseases*

	HLA—B27 Present		*HLA—B27 Absent*		*Total*
	Male	*Female*	*Male*	*Female*	
Ankylosing spondylitis	5	0	1	1	7
Reiter's disease	2	0	0	0	2
Urethritis	0	0	2	0	2
Sacroiliitis	0	1	0	0	1
Osteitis condensuns ilii	0	1	0	0	1
No associated disease	4	7	5	10	26
Total	11	9	8	11	39

study there was an increased incidence of HLA-B27 (42·1 %) among 19 patients with chronic iridocyclitis of adult onset which was significantly higher than that among normal controls ($\chi^2 = 12·4$, $0·0005 > P > 0·003$). Even among the patients whose chronic iridocyclitis never underwent acute exacerbations HLA-B27 was also significantly increased (36·4 %), and this was again statistically significant ($\chi^2 = 5·77$, $0·02 > P > 0·015$). There appears to be a fundamental difference between adult onset iridocyclitis and chronic iridocyclitis in children or chronic cyclitis, both of which have no correlation with HLA-B27 (Ohno *et al.*, 1977). These data would suggest that there are marked differences among the anterior uveitides, although the clinical findings may be somewhat similar.

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Bleb dystrophy of the cornea: Histochemistry and ultrastructure

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SUMMARY Corneal epithelial biopsies from two patients affected with asymptomatic bleb dystrophy were examined by light and electron microscopy. The basis of this disorder appears to be the deposition of a neutral mucopolysaccharide-protein complex as a continuous layer between the basement membrane and Bowman's layer. This material, although homogeneous in light microscopy, has a fine granular ultrastructure. It is friable, and in view of the apparent integrity of the basement membrane/hemidesmosome system it is suggested that the recurrent epithelial erosions which can occur in this disorder result from shearing of this layer. Fissures in the bleb material contain cells which may play a role in its degradation.

A recently described group of superficial corneal disorders includes the fingerprint, net, bleb (Bron and Brown, 1971) and microcystic dystrophies (Cogan *et al.*, 1964). Brown and Bron (1976) have shown that these dystrophies may be associated with recurrent epithelial breakdown. Thus, they were present in 59% of their patients with the recurrent erosion syndrome. Conversely the same authors (1971) had noted previously that 38% of patients with these superficial dystrophies were also afflicted with symptoms of recurrent epithelial dehiscence. These studies naturally suggest that this group of superficial corneal dystrophies is an important precursor of defective epithelial adherence.

The common ultrastructural basis of these disorders (Cogan *et al.*, 1974; Rodrigues *et al.*, 1974; Broderick *et al.*, 1974) is the deposition of an abnormal or excessive fibrillo-granular protein which accumulates deep to the basal cells, and in the respective cases of fingerprint and microcystic dystrophies is found at the midepithelial level as finger-like protrusions or in continuous sheets.

The bleb form of superficial corneal dystrophy was present in 28% of patients with the recurrent erosion syndrome who were examined by Brown and Bron (1976). Although bleb dystrophy may be clinically interrelated with the other forms, its histopathology is unknown. Two recent patients with asymptomatic bleb dystrophy provided an opportunity to investigate its pathogenesis.

Case reports

Case 1. A 50-year-old White male patient who was otherwise healthy complained of irritation and blurred vision affecting his right eye for the previous week. There had been no preceding ocular symptomatology nor was there a significant family history of eye disease.

Examination showed corrected vision OD=20/80, OS=20/20. A dendritic ulcer of the herpes simplex type was present in the epithelium of the right cornea. Profuse subepithelial blebs were present in clusters in the parapupillary zones of both corneae. Their distribution in the left cornea is illustrated in Fig. 1. The blebs, which varied in size, were on the average about 50 μ wide. With the direct ophthalmoscope the blebs had an orange-skin appearance when set against the fundal reflex. Viewed by indirect slit-lamp illumination from the iris the blebs appeared as transparent bubbles with an unreversed lighting effect (Fig. 2), a phenomenon which, as Brown (1971) noted, indicates a refractive index higher than that of the surrounding tissue. In focal illumination the blebs were seen as black dots set in a relucent background. There were no demarcation or other lines in either cornea. In the left eye it was possible to determine that there was no interference with the precorneal tear film and that

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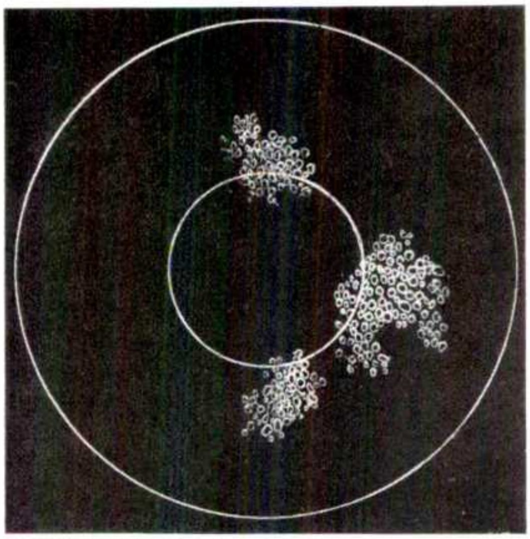

Fig. 1 *Distribution of blebs, left cornea, case 1*

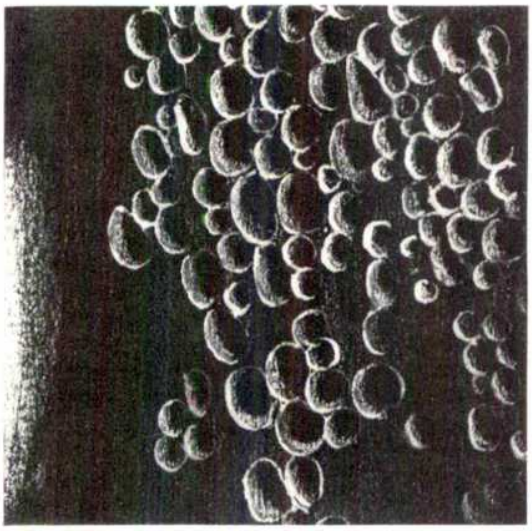

Fig. 2 *Slit-lamp drawing illustrates reversed lighting effect produced when blebs are subjected to indirect retro-illumination from the iris (case 1)*

the blebs were not in register with the corneal mosaic, which was intact. Moreover, sensation to a 1-in long 8×0 nylon thread was unimpaired. Tear and Meibomian secretions of the left eye were clinically normal.

Idoxuridine ointment was administered four-hourly for seven days without clinical improvement. The dendrite and surrounding epithelium were then removed by using a cotton-stick applicator. It was noticed that blebs were adherent to the underside of the ablated epithelium; hence a 2 mm Elliot trephine was used to demarcate two biopsies of the adjacent apparently healthy epithelium and underlying blebs. Corneal healing was complete within four days, and there has been no further evidence of corneal ulceration for the past nine months.

Case 2. A 65-year-old White woman, requiring cosmetic blepharoplasty for senile skin changes, was found to have bilateral bleb dystrophy. She had never experienced symptoms suggestive of the recurrent erosion syndrome, nor was there a family history of this disorder. The blebs, although more extensive than seen in case 1, were in all other respects essentially similar. Corneal sensation and lachrymal and lid secretions were quantitatively normal. The ophthalmoscopic appearance of the blebs on the left side is shown in Fig. 3. With the patient's informed consent a 2 mm biopsy of the corneal epithelium and underlying blebs was undertaken from each eye at the times of blepharoplasty. The corneal epithelial defects healed within 24 hours; there was no residual scarring. There have been no ocular symptoms for the past six months of surveillance.

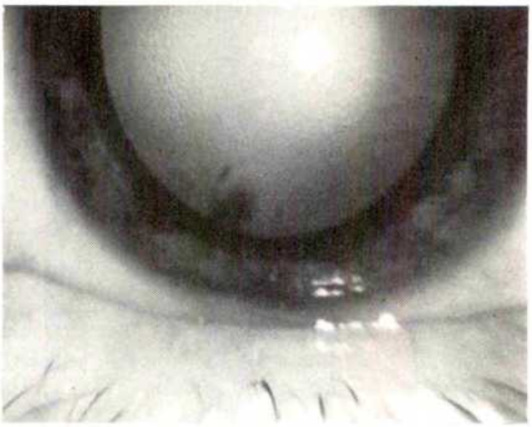

Fig. 3 *Orange-skin effect seen when blebs are focused with ophthalmoscope against the red reflex (case 2)*

Methods

Two of the epithelial biopsies (one from each patient) were fixed in 10% formalin, dehydrated, and then infiltrated with paraffin wax. Paraffin sections were treated with a variety of tinctorial and histochemical techniques which will be mentioned alongside the results obtained. The other two specimens were prepared for transmission electron microscopy (TEM), the examination being under-

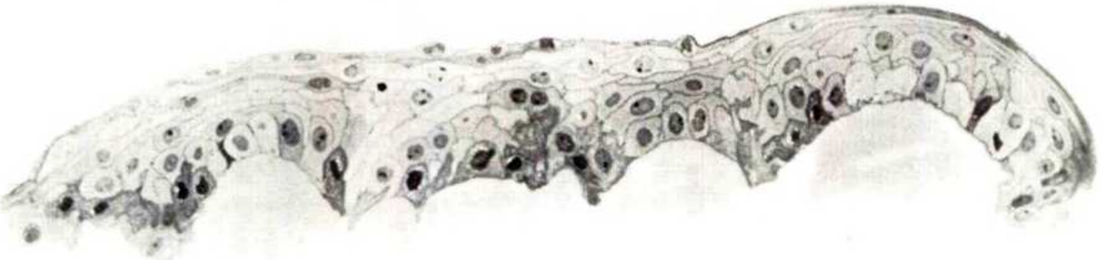

Fig. 4 *Deep surface of corneal epithelium is invaginated by mounds of bleb material. Bleb dystrophy, montage, toluidine blue,* × *300*

taken with an RCA Emu 3G instrument. The disc from case 1 was placed in $2\frac{1}{2}\%$ cold glutaraldehyde prior to osmification, whereas the specimen from case 2 was fixed in cold Karnovsky's (1965) fluid and then treated with a solution of 2% osmic acid and 2% ruthenium red in accordance with Luft's (1965) method for mucopolysaccharides. Both specimens were ultimately embedded in epoxy resin. Orientational sections from the specimens embedded in resin were stained with toluidine blue and viewed by light microscopy, while suitably thin sections were stained with lead citrate and uranyl acetate. Skin obtained at blepharoplasty from case 2 was formalin-fixed and embedded in formalin. Subsequent sections were stained routinely.

Observations

LIGHT MICROSCOPY

Skin biopsies show predictable age changes, but there are no abnormal accumulations of periodic acid-Schiff (PAS) positive material in the region of the basement membrane, which appears normal.

The four corneal biopsies consist of corneal epithelium, basement membrane, and a subepithelial deposit of 'hyaline' material.

The corneal epithelium is invaginated on its deep surface by mounds of a homogeneous material which appears pink in haematoxylin and eosin preparations but is pale blue after staining with toluidine blue (Fig. 4). Occasional mounds show fissures in which flattened cells with elongated processes are found (Fig. 5). The bleb material bordering these fissures is often less intensely stained than elsewhere. The basement membrane of the cornea appears intact and of normal thickness. Corneal epithelium overlying the mounds is healthy apart from the presence of a few darkly stained cells in the basal layer.

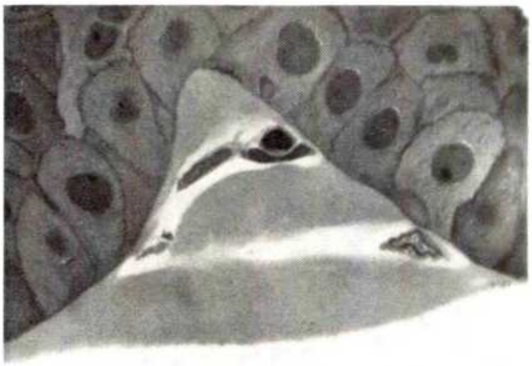

Fig. 5 *Zone of well-defined rarefaction borders fissures in the bleb material. Several cells occupy the fissures. Bleb dystrophy, toluidine blue,* × *1250*

The table summarises the results of various histological and histochemical methods on the basement membrane and subepithelial bleb material.

PAS positivity of the bleb material is not affected by pretreatment of the sections with either diastase or hyaluronidase (at pH 2 and pH 4). Both basement membrane and the subepithelial 'hyaline' material are monorefringent in polarised light.

Table

	Basement membrane	*Subepithelial bleb material*
Millon reaction	Positive	Positive
Toluidine Blue	Lavender metachromasia	Ortho-chromatic
PAS	Strongly positive	Positive
Sudan black B	Negative	Negative
Gomori reticulin stain	Positive	Negative
Congo Red (dichroism) amyloid stain	Negative	Negative
Thioflavin T (fluorescence) amyloid stain	Negative	Negative

TRANSMISSION ELECTRON MICROSCOPY

Apart from the intracytoplasmic vesicles in some of the basal cells, which may well be artifactual, and the presence of rare electron-dense acantholytic cells in this layer, the corneal epithelium does not exhibit any cytologic abnormality. The basal cells lie on a normal basement membrane, which has its usual complement of hemidesmosomes (Fig. 6). The bleb material is composed of fine granules measuring about 70 Å. In sections from the biopsy treated with ruthenium red the bleb granules exhibit no increase in electron density. Irregularly banded fibrils which are orientated perpendicularly form an incomplete seam beneath the basement membrane. No spatial relationship exists between the bleb configuration and the subepithelial disposition of these fibrils. In places where the plane of biopsy cleavage has been deep enough it can be determined that the bleb material is not confined to the mounds, but forms a continuous subepithelial layer. Near the edges of the specimen occasional spherical accumulations of bleb material appear to lie entirely within the epithelium. These accumulations are not surrounded by basement membrane and have presumably been displaced from the subepithelial layer by the trauma of biopsy.

Occasional blebs show horizontal fissures which are partially occupied by unidentified cells (Fig. 7). These cells have numerous thin cystoplasmic processes, in which tonofibrils are a prominent component. They are richly endowed with membrane-bound vesicles containing sparse granular material. In places the vesicles are aligned near the cell membrane, where some of them open on to the surface (Fig. 8). Bleb granules in the vicinity of these cells are frequently absent or else considerably reduced in number, producing a pericellular zone of rarefaction which is sharply demarcated from the main mass of bleb granules. The granules which are present in these rarefied zones have a smudged appearance and tend to be aggregated in a linear manner.

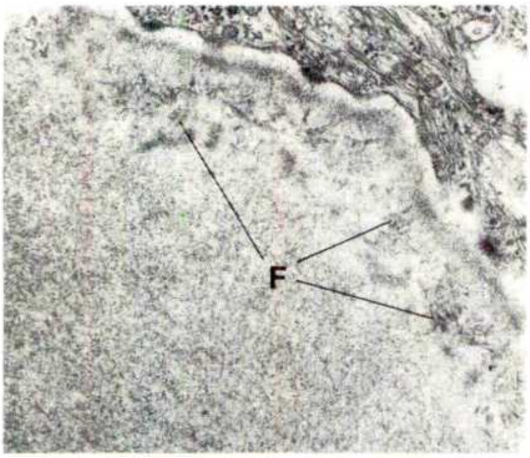

Fig. 6 *Intact basement membrane/hemidesmosome system separates basal cell* (E) *from the granular bleb material. An incomplete seam of vertically orientated fibrils* (F) *lies beneath the basement membrane. Bleb dystrophy (lead citrate/uranyl acetate), TEM,* × *71 000*

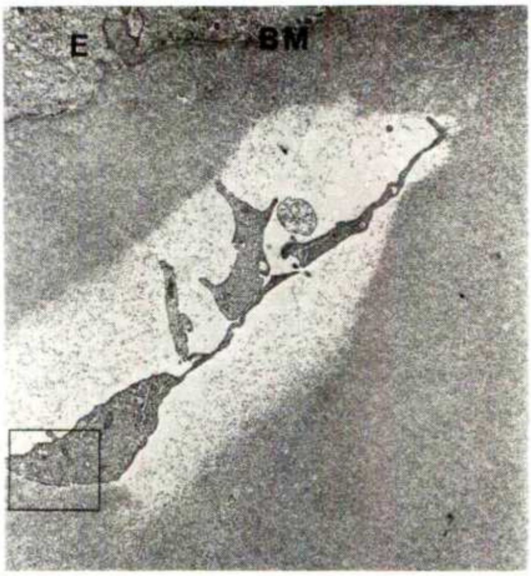

Fig. 7 *Part of cell embedded in bleb material is surrounded by sharply defined zone in which granules are either sparsely distributed or absent.* E. *Basal epithelial cell;* BM *basement membrane, bleb dystrophy (ruthenium red), TEM,* × *10 000*

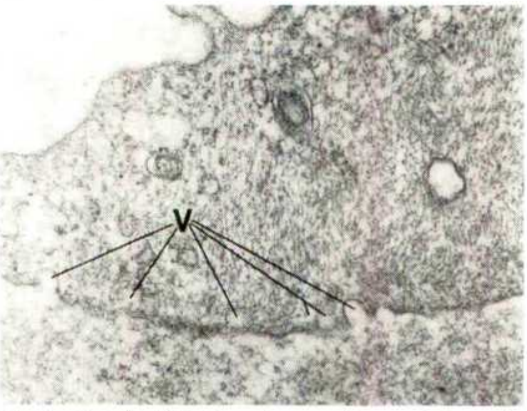

Fig. 8 *Detail of Fig. 6 to show membrane-cald vacuoles V arranged close to the cell membrane. Some of the vacuoles have opened extracellularly. Bleb dystrophy (ruthenium red),* × *71 000*

Discussion

The histological substrate of bleb dystrophy, as adduced from the present study, is the accumulation of a continuous layer of fibrillo-granular protein between the basement membrane of the epithelium and Bowman's layer. The outer surface of this material is moulded in the form of hemispherical mounds or blebs which indent the overlying epithelium without deforming its superficial layers. The epithelial basement membrane together with its hemidesmosomal attachments is normal in form and staining reactions. The bleb material has for the most part a finely granular ultrastructure, but alongside the basement membrane irregularly banded fibrils form a discontinuous seam. These filaments appear to correspond with special fibrils of the dermis described by Palade and Farquhar (1965) which have an anchoring role. Corneal epithelial cells overlying the blebs, although displaced or distorted, in general show little ultrastructural abnormality, but occasional basal cells are acantholytic and electron-dense. Similar cells were noted in the corneal epithelium in fingerprint dystrophy by Brodrick *et al.* (1974). In the latter condition these cells were relatively common and resulted in microcyst formation, which is not seen in bleb dystrophy unless epithelial erosion has occurred.

Subepithelial granular material in Cogan's microcystic dystrophy, which is morphologically similar to that seen in the present study of bleb dystrophy, has been described as 'basement membrane-like' by Cogan *et al.* (1974). The present study does not provide evidence for this assertion. It demonstrates on the contrary that the subepithelial material contains only a few fibrils which have formed in the presence of a normal basement membrane/hemidesmosomal system. Moreover, unlike basement membrane, it has no affinity for Gomori's reticulin stain. Studies with fluorescent antibody conjugates raised against both mesodermal and ectodermal basement membranes and other proteins may resolve this question. The bleb material exhibits PAS positivity, which resists digestion with diastase; these findings together with its lack of ruthenium red reactivity suggest the presence of a neutral polysaccharide-protein complex.

The presence of unidentified cells which lie in rarefied seams of the bleb material is a striking feature present in a minority of the blebs (Figs. 4, 6, and 7). The seams which contain a few granules, the outlines of which are often smudged, are sharply demarcated from the main mass of compact bleb material. Numerous cytoplasmic vesicles are present in these cells (Fig. 7). In some instances the vesicles are aggregated in a row alongside the plasma membrane, where a few of them are open on to the cell surface. It is tempting to speculate that these cells are synthesising a cathepsin which is degrading the bleb granules, but the evidence is circumstantial. It seems wiser to defer any generalisations about cell morphology and the possible secretion of enzyme until the nature of the bleb material is clearer.

A defective basement membrane was noted in traumatic recurrent erosion by Goldman and others (1971) and in spontaneous recurrent erosion by Tripathi and Bron (1972), who also noted a paucity of hemidesmosomes. In contrast, the present study of bleb dystrophy indicates integrity of the basement membrane hemidesmosomal system. Moreover, a similar observation was made in the fingerprint disorders both of dystrophic type by Brodrick *et al.* (1974) and of that sometimes seen in metaherpetic keratitis by Brodrick and Dark (1976). Surgical removal of the epithelium in all three conditions resulted in shearing of the subepithelial granular material. Thus it is possible that epithelial erosion associated with some of the superficial dystrophies is a sequel to splitting of this abnormal subepithelial layer of granular material without involving defects in the basement membrane or its anchorage system. If this is indeed the primary mechanism in such cases, then surgical treatment, when indicated, should aim at removing this friable material from the anterior surface of Bowman's layer.

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Orbital cyst due to *Histoplasma duboisii*

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SUMMARY A cystic swelling in the orbit due to *Histoplasma duboisii*, clinically thought to be a dermoid cyst, is described.

Histoplasmosis due to *Histoplasma duboisii*, known as African histoplasmosis, may occur localised as a solitary nodule, as a bone lesion, or in disseminated form involving skin, subcutaneous lymph nodes, bones and joints and abdominal viscera, and rarely the lungs (Vanbreuseghem, 1953, 1956).

Intraocular involvement has been described in some cases of the classical American histoplasmosis due to *Histoplasma capsulatum* (Krause and Hopkins, 1951; Van Metre and Maumenee, 1964; Schlaegel and Kenney, 1966). So far only one case has been reported of acute infection of lacrimal gland and adjacent parts of frontal and zygomatic bones caused by *H. duboisii* (Olurin *et al.*, 1969). The present communication reports another case of orbital histoplasmosis due to *H. duboisii*, presenting as a silent solitary cystic swelling with erosion of supraorbital margin.

Case report

A 20-year-old Igbo welder presented with a swelling in the right supraorbital region of probably two months' history. It started as a small nodule, painless, and without any history of injury.

On examination there was a localised, slightly firm, well defined cystic swelling (2 × 2 cm). It was not tender, and was slightly mobile but with skin moving freely over it. The upper border of swelling appeared to erode the supraorbital margin. The posterior wall was not palpable. The visual acuity was normal, right eye 20/15, left eye 20/15. There was no other ocular lesion. *X*-ray examination of orbit showed erosion of the supraorbital margin. No cutaneous lesion was found. Systemic examination and *x*-ray of chest were normal. On clinical assessment it was provisionally diagnosed as a case of dermoid cyst.

Surgery

A supraorbital incision was made and a very well defined cystic swelling was exposed. The wall of the swelling was seen to be fixed at the upper border and deep surface. The cyst ruptured, and thick blood-stained pus was evacuated. The wall of the cyst was removed in pieces and sent for histological examination.

Histology

The cyst wall was devoid of any epithelial lining but appeared to be composed in part of fibro-collagenous tissue. Around the cyst wall numerous yeast cells (7 to 15 μm in diameter) typical of *Histoplasma duboisii* (Figs. 1, 2) were observed within giant cells

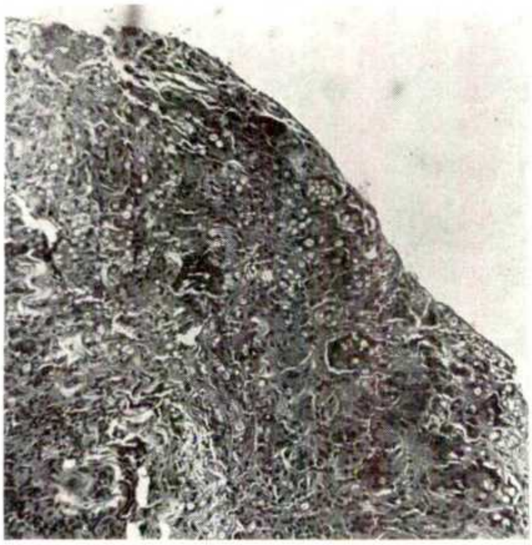

Fig. 1 *Low magnification × 140*

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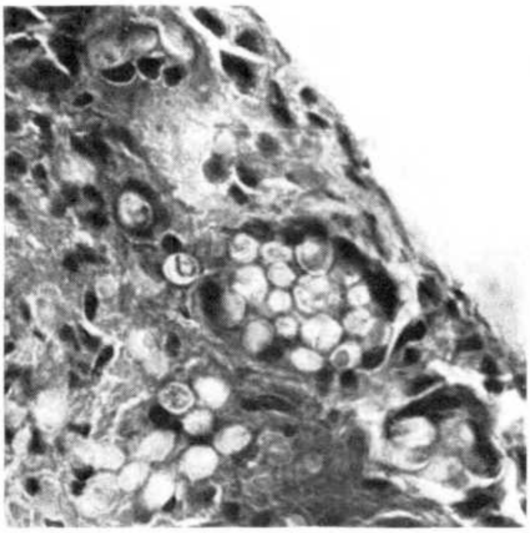

Fig. 3 *High magnification ×475. Section through the cyst showing* H. duboisii *cell within and outside giant cell. The cyst wall is devoid of any epithelial lining*

as well as occurring extracellularly along with macrophages, plasma cells, and lymphocytes.

Discussion

Ocular histoplasmosis is mainly caused by *Histoplasma capsulatum* and usually presents in the form of uveitis or chorioretinitis. Another form of histoplasmosis has now been recognised caused by *H. duboisii,* which presents clinically and histologically in a different way. Previously only one case of orbital histoplasmosis due to *H. duboisii* has been described in a young girl as a localised acute inflammation (Olurin *et al.,* 1969). In the present case there was no evidence of ocular inflammation at any stage.

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British Journal of Ophthalmology, 1977, **61**, 72

Book reviews

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Slit-lamp photography of the anterior segment forms a valuable part of the investigation and assessment of disturbances in this region and it is important in teaching. This well-illustrated volume describes in detail the techniques of this procedure and evaluates the different types of apparatus and film.

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R. A. WEALE

Obituary

Basil Graves, MC, MA, MRCS, LRCP, FACS, DOMS

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After reading natural sciences at Cambridge, Basil Graves proceeded to Charing Cross Hospital and qualified with the Conjoint diploma in 1915. As regimental medical officer to the 13th Battalion of the Royal Fusiliers he was awarded the Military Cross for conspicuous gallantry. He passed through the House at Moorfields Eye Hospital and later became the Lang research scholar. For some time he was honorary surgeon to St Paul's Eye Hospital, Liverpool, but later forsook this appointment and spent the rest of his active life in Luton. He is survived by his wife and two daughters.

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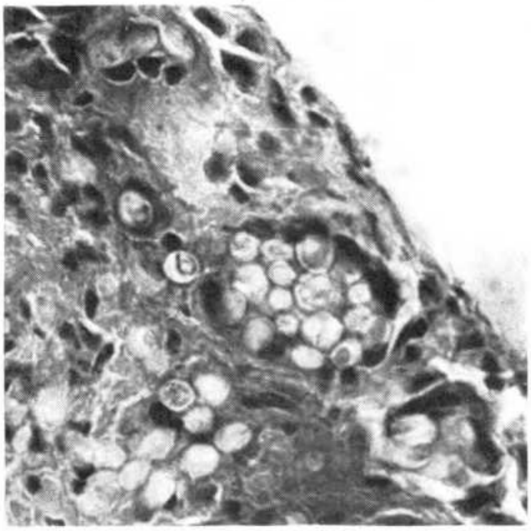

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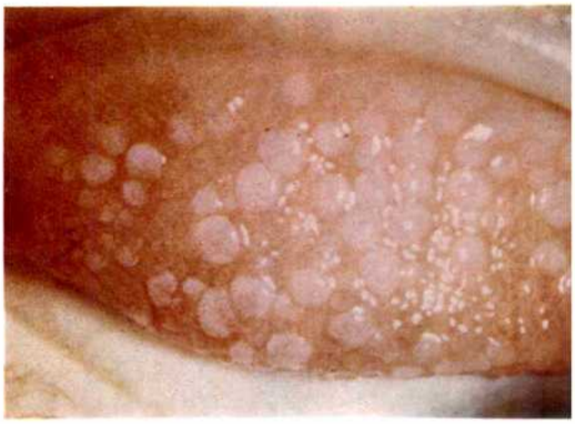

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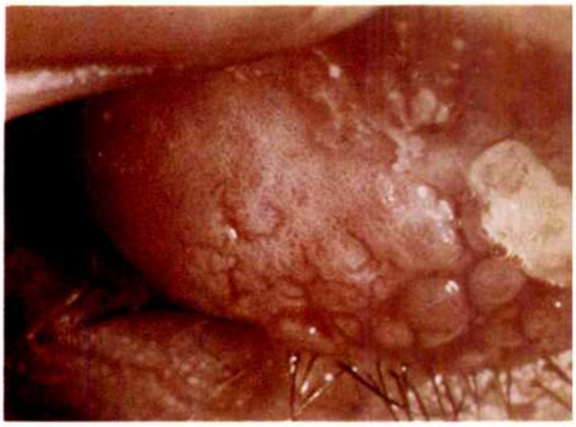
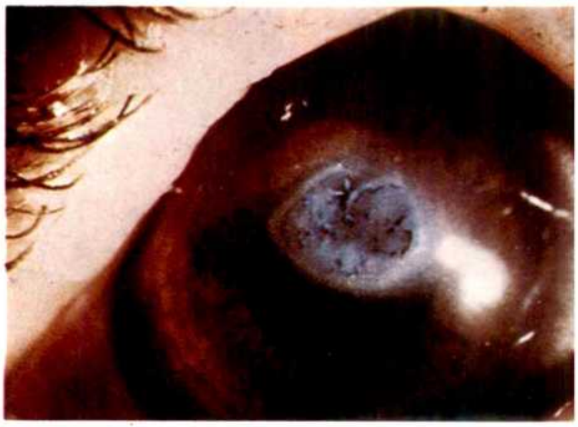


Upper tarsal plate in active vernal disease. Note fine lace-like scarring and profuse mucopurulent discharge.



Indolent vernal corneal ulcer stained with alcian blue to demonstrate mucous deposition.

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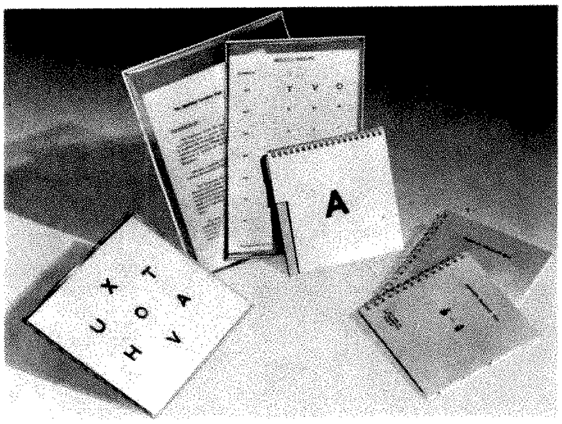

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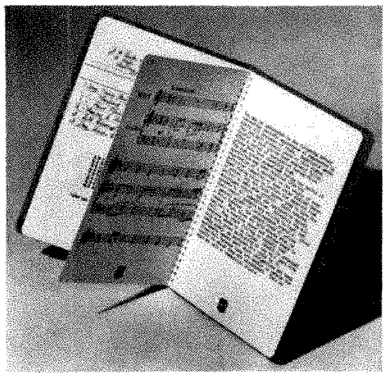

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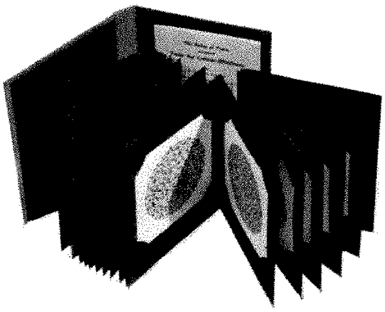

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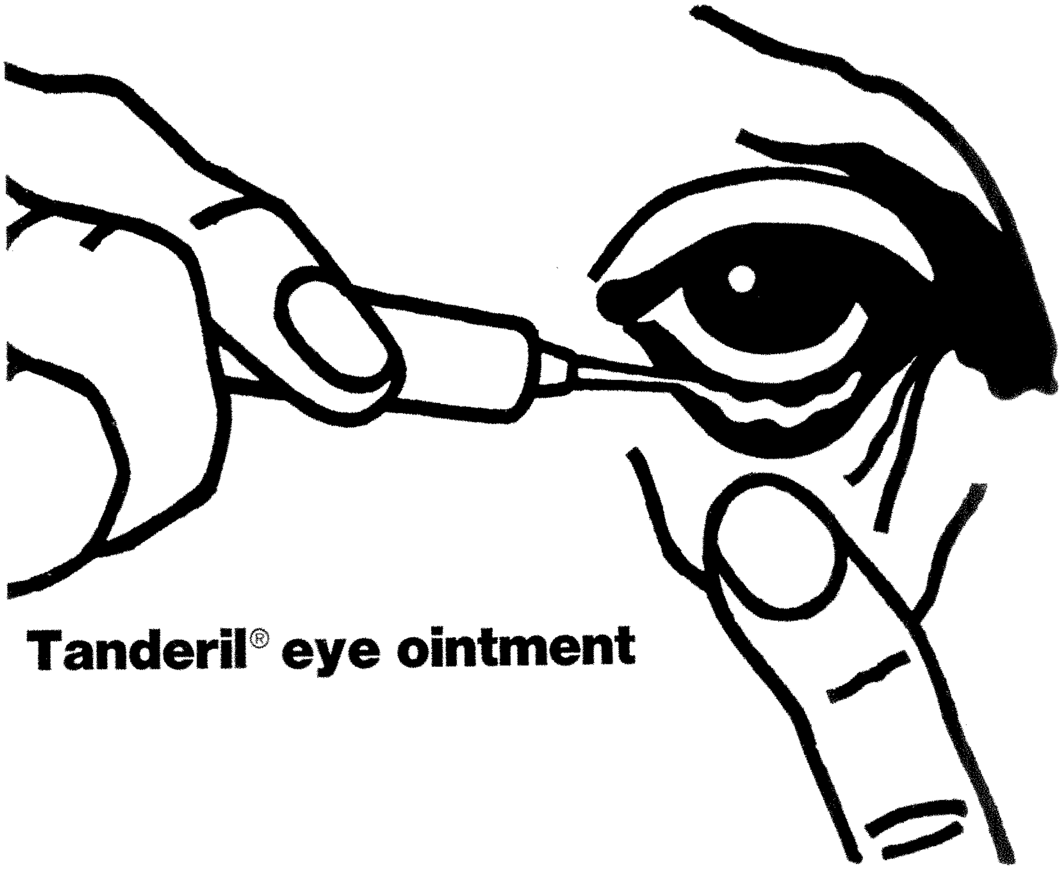

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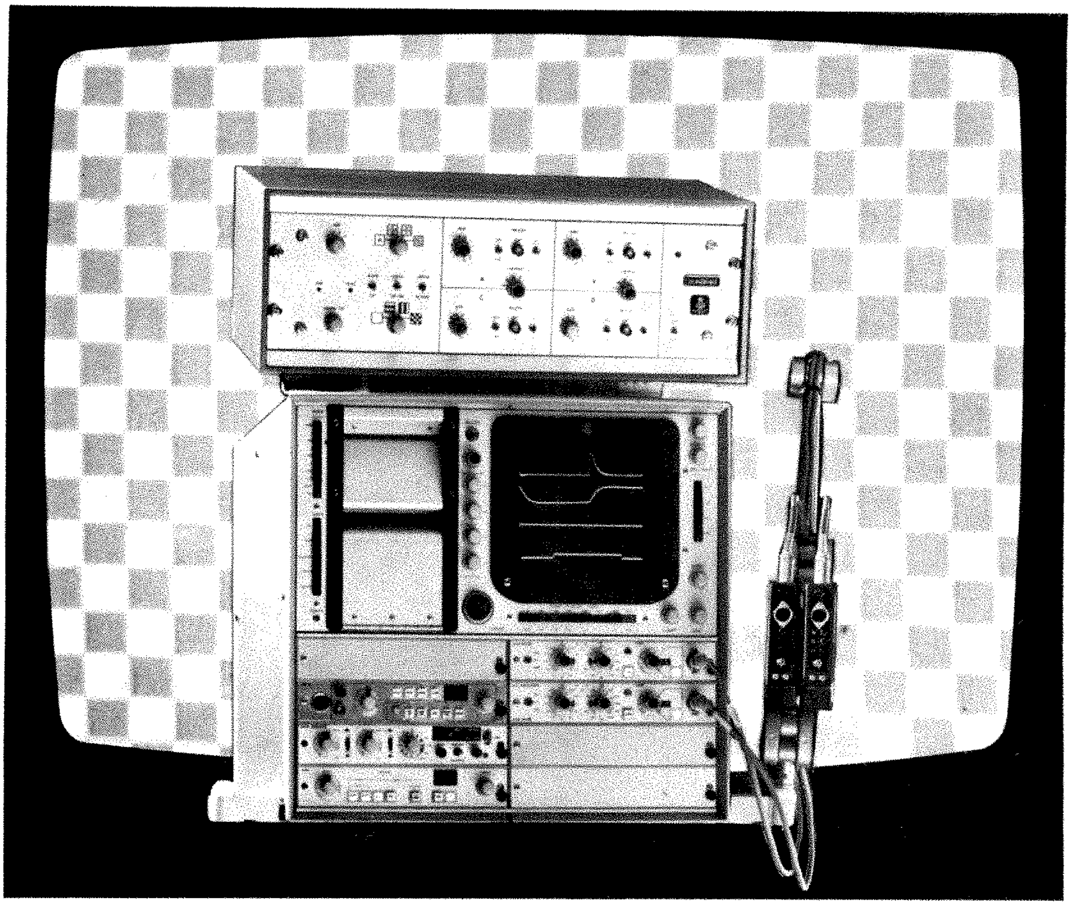

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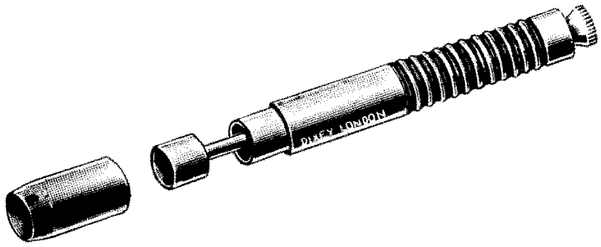

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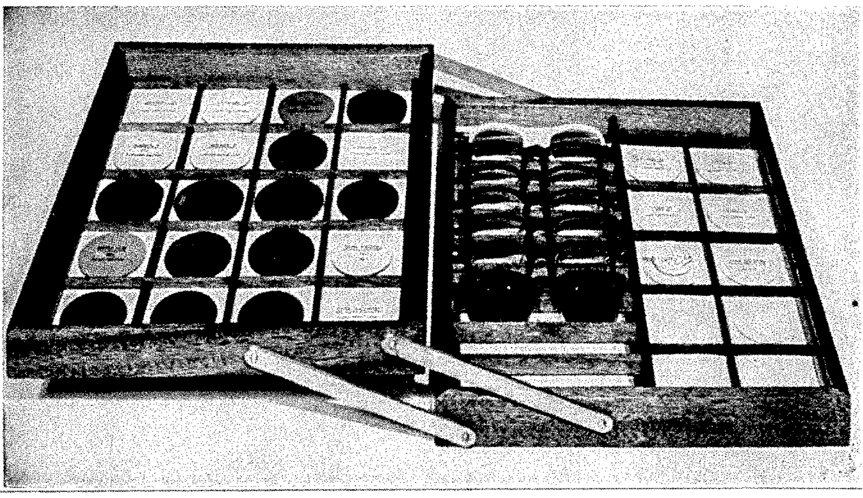

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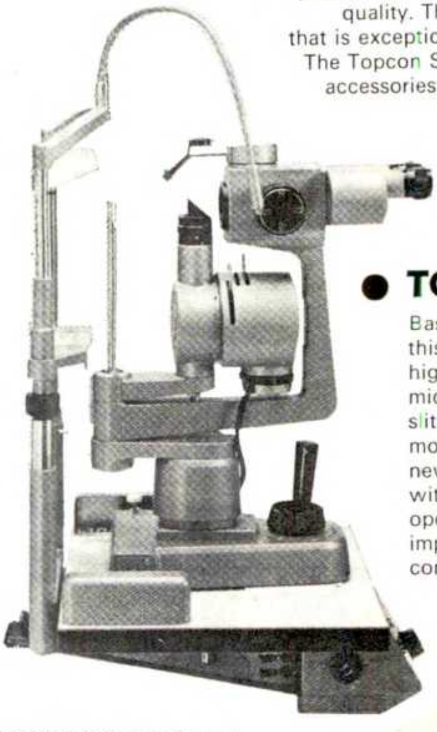

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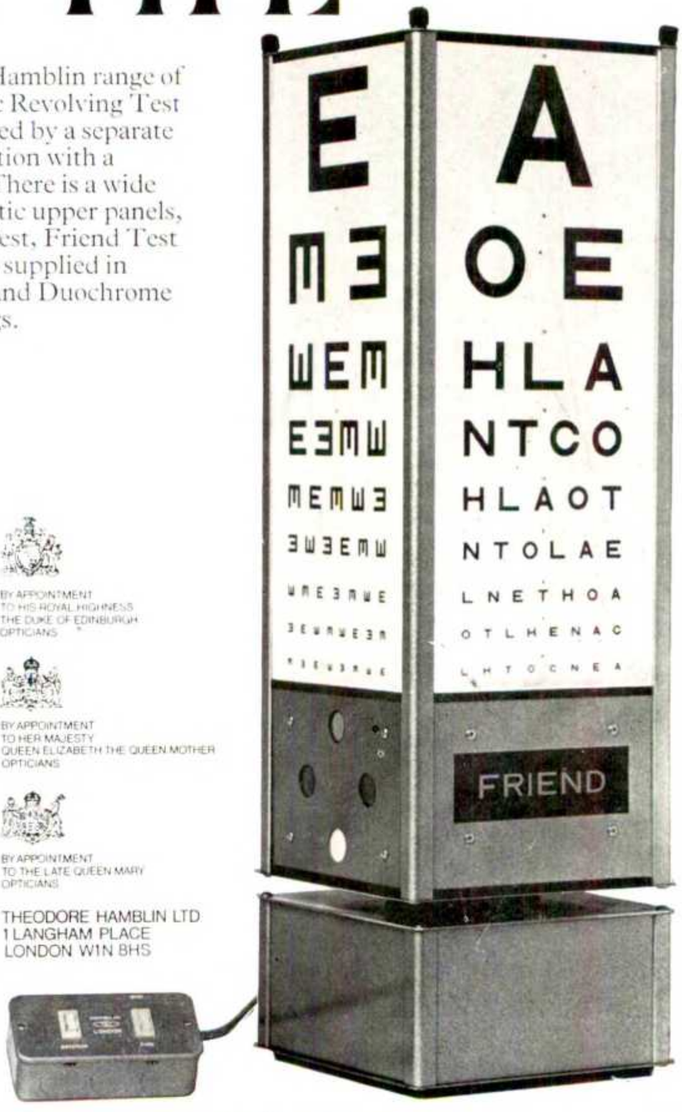

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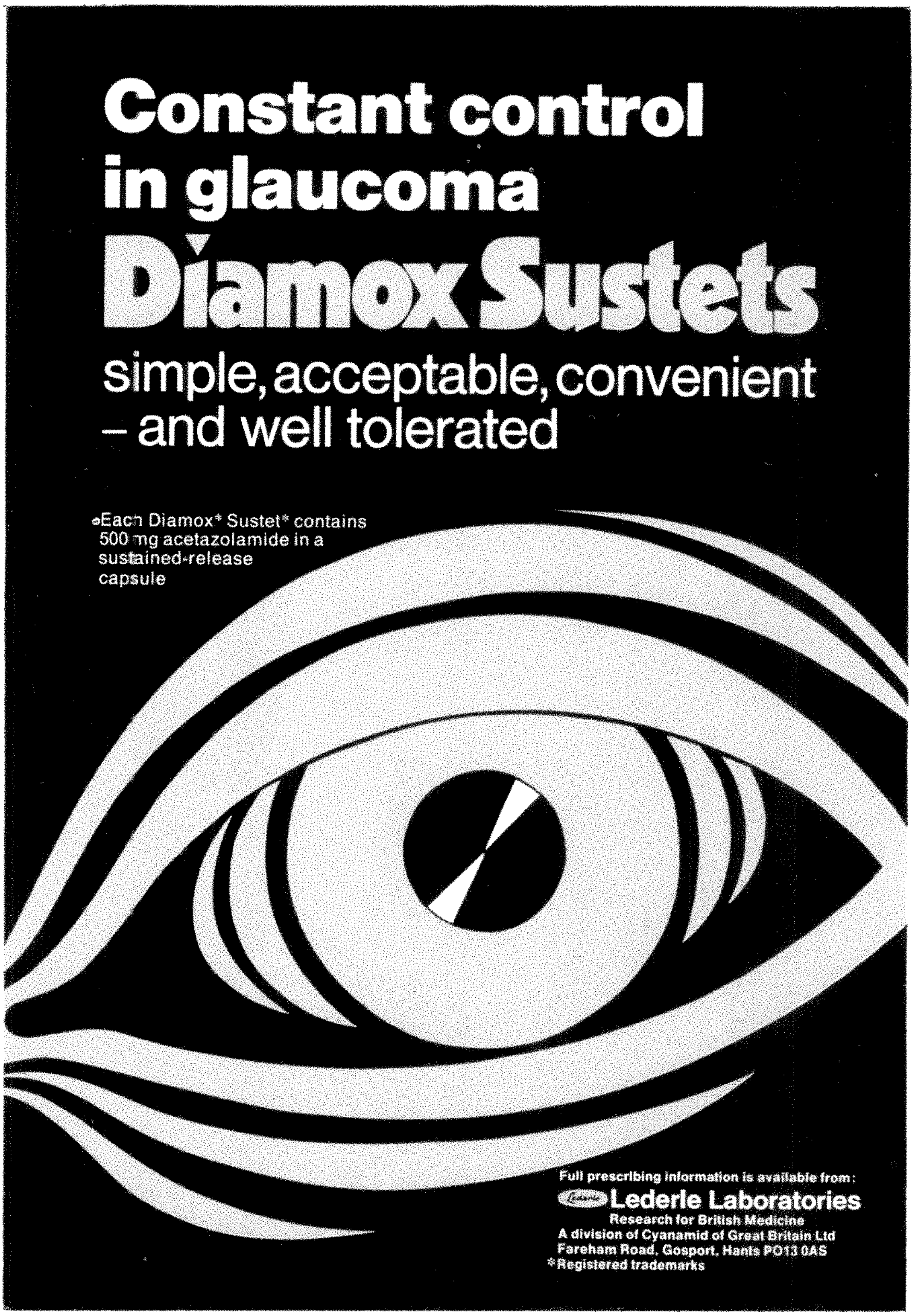

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British Journal of Ophthalmology, 1977, **61**, 73–75

Editorial: Adenovirus keratoconjunctivitis

Adenovirus (adeno) is responsible for a large proportion of sporadic cases of keratoconjunctivitis (KC) and for outbreaks of the disease in hospitals, schools, and factories. The eye infection is characterised by a moderate to severe KC, causing in a proportion of the patients hazy vision lasting several years. In the United Kingdom the eye infection is a major economic problem and is probably responsible for the loss of tens of thousands of working days each year.

Epidemic keratoconjunctivitis (EKC) caused by adeno 8 is a well described entity (Bietti and Bruna, 1957; Jawetz *et al.*, 1957; Leopold, 1957; Thygeson, 1957; Davidson, 1964; Imre *et al.*, 1964; Liabson *et al.*, 1968; Grist *et al.*, 1970; Dawson *et al.*, 1972; Hart *et al.*, 1972). Severe outbreaks of EKC are especially common in hospitals and factories (Leopold, 1957; Thygeson, 1957; Davidson, 1964; Liabson *et al.*, 1968). Adenos 3 and 7 are the most common causes of sporadic KC. Other types, i.e., 1, 2, 4, 5, 6, 9, 10, 11, 13, 14, 15, and 29, are also reported to cause moderate to severe KC (Bell, 1957; Hogan, 1957; Huebner and Rowe, 1957; Kendall *et al.*, 1957; Kimura *et al.*, 1957; Ormsby *et al.*, 1957; Jones, 1962; Caldwell *et al.*, 1974; Tanifuji *et al.*, 1974; Muzzi *et al.*, 1975). Adeno 19 has recently been recognised as a cause of KC similar to EKC (Hierholzer *et al.*, 1974; O'Day *et al.*, 1976; Darougar *et al.*, 1977).

Adeno KC commonly affects adults between the ages of 20 and 40 years and is more common in males than females (2:1). No seasonal variation is observed for sporadic cases except for adeno 7, which appears to be more common in the summer.

Man appears to be the only reservoir of the infection. Upper respiratory tract infection due to adenovirus (pharyngoconjunctival fever) is a common disease, especially among children. Adenovirus has also been isolated from the tonsils and adenoid tissues of the throat in patients with no apparent inflammation (Huebner and Rowe, 1957; Vargosko *et al.*, 1965). Transmission from respiratory tract to the eye is responsible for the majority of sporadic adeno KC. Eye-to-eye transmission is the common cause of outbreaks of adeno KC. The virus can commonly be isolated up to 2 weeks from the onset of the keratoconjunctivitis. The virus has also been isolated from chronic papillary conjunctivitis (Darougar *et al.*, 1977). Associated systemic infections occur in 50% of the patients with adeno KC. The majority of these suffer from a pharyngitis and rhinitis. A few may develop general malaise with a fever or gastrointestinal upset with diarrhoea and vomiting. Preauricular lymphadenopathy occurs in approximately 90% of cases.

The incubation period for adeno KC is usually 7 to 9 days but ranges between 2 and 14 days. The infection starts unilaterally, and in the majority of cases the other eye develops conjunctivitis 2 to 7 days later.

The KC is generally mild to moderate in patients infected with adeno 2, 3, 4, 15, and 29, but slightly more severe in cases of adeno 7 infection. Adeno 5, 8, and 19 cause most severe disease. The average duration of conjunctivitis is 4 to 6 weeks for adeno 5, 8, and 19, and slightly shorter for other serotypes.

Foreign body sensation, photophobia, lachrymation, discharge, swelling, and inflammation are the main symptoms.

On clinical examination, the bulbar conjunctiva is hyperaemic with chemosis. Haemorrhages may occur in the cases of adeno 8 and 19. The major signs in the palpebral conjunctiva are moderate to severe hyperaemia, diffuse infiltration, papillary and follicular hypertrophy. Papillary hypertrophy is more severe in the upper tarsal conjunctiva and may be present for 2 to 4 weeks in most cases except for adeno 5, 8, and 19. Occasionally the papillary reaction may continue for several months (Darougar *et al.*, 1977). Follicular hypertrophy is moderate and is present mainly in the upper and lower fornices. Punctate haemorrhages and pseudomembrane are common in severe cases of adeno 8 and 19 and less in adeno 3 and 7. Moderate to severe scarring may develop 20 to 30 days after the onset of infection in patients who had had well marked pseudomembrane.

Keratitis is common in adenovirus infection. Mild to moderate epithelial punctate keratitis (EPK: small, punctate, slightly elevated corneal infiltrations) (Jones, 1962) may develop in the early stages of infection with all types of adenovirus. The duration of EPK is less than 3 weeks except in cases of adeno 8 and 19. Subepithelial punctate keratitis (SEPK: large, dense, well marked opacities in the subepithelial area of the cornea) (Jones, 1962) may develop in association with adeno 3, 4, 5, 7, 8, and 19. The SEPK may resolve within 3 months in all cases of adeno KC, except for adeno 8 and 19, which may remain for several years. Diffuse stromal infiltration (resembling disciform keratitis) and corneal oedema may occur in association with severe keratitis. A mild anterior uveitis may also develop in cases of severe adeno 8 and 19.

Outbreaks of adenovirus KC are a continuing problem in hospitals, outpatient departments, surgeries, schools, and in swimming pools. Adeno 3, 7, 8, and 19 are the commonest cause of these outbreaks (Hogan, 1957; Kendall *et al.*, 1957; Leopold, 1957; Thygeson, 1957; Davidson, 1964; Liabson *et al.*, 1968; Caldwell *et al.*, 1974; Tanifuji *et al.*, 1974; O'Day *et al.*, 1976; Darougar *et al.*, 1977). Institutional transmission may result from contamination of eye solutions, instruments, including slit-lamp and tonometers, and by contaminated fingers of doctors and nurses. Transmission among patients may be due to direct contact or by droplet spread. Outbreaks of adeno KC are prevented by segregation of patients with infective eye disease, increased care with hand washing with soap before and after examination, the use of single dose eye solutions or change of droppers for each patient, and proper sterilisation of instruments, especially tonometers.

The clinical features of adeno KC—a moderate to severe bilateral follicular conjunctivitis, subepithelial punctate keratitis, and associated upper respiratory infection—are helpful in the diagnosis of infection. However, differential diagnosis should be made from herpetic keratoconjunctivitis, epidemic haemorrhagic conjunctivitis (picornavirus), and chlamydial and bacterial conjunctivitis.

Laboratory tests may help diagnosis of adeno KC. In the acute stage of infection the presence of profuse mononuclear cells, especially lymphocytes, in conjunctival scrapings is highly suggestive of a viral infection. Fluorescent antibody (FA) staining of conjunctival smears provides a rapid and sensitive method for the detection of adenovirus in conjunctival cells (Imre *et al.*, 1964; Schwartz *et al.*, 1976). Cultural tests for isolation of adenovirus are rather slow and may require between 1 and 8 weeks for detection and identification of the virus. The highest rate of isolation is obtained in the first 2 weeks of KC. The complement fixation test is a standard serological test for detection of group antibody to adenovirus. A four-fold rise in the titre of antibody between the acute and convalescent sera is significant for diagnosis of adenovirus KC.

Although adenovirus is a DNA virus that has some *in vitro* sensitivity to idoxuridine and trifluorothymidine, no effective chemotherapy has yet emerged for this important cause of ocular and respiratory morbidity. Frequent topical applications of antibiotic drops may soothe the eye and prevent secondary bacterial infection.

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British Journal of Ophthalmology, 1977, **61**, 76–85

Epidemic keratoconjunctivitis and chronic papillary conjunctivitis in London due to adenovirus type 19

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From the Department of Clinical Ophthalmology, Institute of Ophthalmology and Moorfields Eye Hospital
D. A. McSWIGGAN
From the Public Health Laboratory and Department of Microbiology, Central Middlesex Hospital

SUMMARY Since July 1973 cases of keratoconjunctivitis resembling epidemic keratoconjunctivitis were observed in the External Eye Disease Clinic at Moorfields Eye Hospital, City Road, London. Adenovirus type 19 was isolated in human embryonic kidney cells from 21 patients. The majority were males between 20 and 40 years old. A small hospital outbreak involving six patients occurred.

Clinical features of the disease, consisting of moderate to severe follicular conjunctivitis, major subepithelial punctate keratitis, sometimes with pseudomembrane and scarring, were closely similar to those of epidemic keratoconjunctivitis caused by adenovirus type 8. This similarity, as well as the ability of the agent to cause hospital outbreaks, indicates that adenovirus type 19 is a cause of epidemic keratoconjunctivitis.

A case of bilateral chronic papillary conjunctivitis that persisted for 16 months following an acute onset was described. Adeno 19 was isolated from the eye of the patient after 12 months of recrudescent or recurrent illness. Chronic adenovirus infection lacking the usual clinical picture of an acute follicular reaction has not hitherto been described. Such cases are probably important because of the obvious danger of continuing the carriage and shedding of infective adeno 19 from one outbreak to another, by presenting subsequently in eye clinics, and providing an unrecognised source of infection to initiate further outbreaks of hospital transmission.

During the year 1973–74 it became apparent that an increase was occurring in the number of sporadic cases of acute keratoconjunctivitis with subepithelial punctate keratitis presenting in the External Eye Diseases Clinic, Moorfields Eye Hospital, London. Adenovirus type 19 (adeno 19) was isolated from a number of these cases. The epidemiological and clinical features of the disease appeared to be similar to those of epidemic keratoconjunctivitis (EKC) caused by adenovirus type 8 (adeno 8).

Adeno 19 was first isolated in 1955 from the eye of a Saudi Arabian child with active trachoma (Bell *et al.*, 1960). Systemic infection by this serotype has been rare: in England and Wales during the period of 1969–72 only one isolate of adeno 19 was reported from the respiratory tract (Communicable Diseases Report, 1974). However, since the summer of 1973 several outbreaks, or sporadic cases, of adeno 19 keratoconjunctivitis have been reported in the USA (Hierholzer *et al.*, 1974), Canada (Vas *et al.*, 1974), Belgium and Holland (Desmyter *et al.*, 1974), and Scotland (Bell and Winton, 1975).

This paper presents the epidemiological and clinical features of adeno 19 keratoconjunctivitis observed in London and stresses the risks of hospital outbreaks of severe conjunctivitis with major punctate keratitis resembling EKC. It also records the isolation of adeno 19 from a chronic relapsing case of papillary conjunctivitis that would hitherto not have been suspected of being due to adenovirus, and so would offer considerable risk of initiating a new outbreak of hospital-based transmission of infection.

Methods and materials

CLINICAL EXAMINATION

The 21 patients in this study were selected on the basis of positive cultures of adeno 19 from among those referred to the External Eye Disease Clinic at Moorfields Eye Hospital for investigation of acute conjunctivitis.

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Symptoms and clinical signs observed with a Haag Streit 900 slit-lamp were recorded on a proforma using an extension of the method used for the study of trachoma (Dawson *et al.*, 1975).

Laboratory investigations

DIFFERENTIAL CYTOLOGY

Conjunctival impressions were taken using a specially designed plastic spatula (Thatcher, Darougar, and Jones, in preparation). They were fixed with methanol, stained with Giemsa's method, mounted on glass slides, and examined microscopically.

VIRUS ISOLATION

Forty-two specimens were collected, by swabbing different areas of the conjunctiva with cotton wool swabs, from 21 patients. The swabs were placed in plastic capsules with 2SPS transport medium (Darougar and Jones, 1971) and stored in a liquid nitrogen refrigerator until transferred to a –70°C refrigerator in the laboratory.

Each clinical specimen was inoculated into two tubes containing human embryonic kidney (HEK) cells and examined for the presence of cytopathic effect (CPE) up to 21 days (McSwiggan *et al.*, 1975). The isolates were identified by the standard neutralisation test.

SEROLOGY

Serum collected from 15 of these patients by venepuncture at intervals of two to three weeks was tested by a complement fixation test (CFT) for adenovirus group antibody.

Results

SEX AND AGE DISTRIBUTION

The ratio of males to females was 15 to 6. The ages of these patients ranged from 5 weeks to 59 years, but most were between 20 and 40 years old.

SEASONAL VARIATION

Of these 21 patients four were observed in June or July 1973, five between November 1973 and January 1974, 10 in June to August 1974, and two in October or November 1974. The highest incidence in June to August 1974 was partly due to an outbreak of cross-infection in the hospital. Several more cases of a similar nature were observed during this period, but no adenovirus was isolated from them.

SOURCE OF INFECTION

Of these 21 patients two had been in close contact with a friend who had been suffering from conjunctivitis, and six became infected in hospital. The other 13 had not been aware of contact with conjunctivitis or upper respiratory infection in families, friends, or workmates, nor had they attended hospitals or clinics or visited a swimming pool.

HOSPITAL OUTBREAK

In the early summer of 1974 cross-infection occurred at Moorfields Eye Hospital (Fig. 1). A 5-week-old baby who had been attending with TRIC ophthalmia neonatorum, from which *Chlamydia trachomatis* was isolated, apparently contracted adenovirus infection in the Clinic. Four days after a clinical examination the baby developed a moderately severe exacerbation of inflammation in both eyes. The mother of this baby and his 2½-year-old sister each developed conjunctivitis, seven and nine days respectively, after the onset of disease in the baby. Adeno 19 was isolated from the eyes of all three patients.

Another ophthalmologist in the clinic apparently contracted adenovirus infection from a close friend who had been suffering from a severe conjunctivitis with subepithelial keratitis suggestive of an adenovirus infection. While he was incubating the infection, he examined a 16-year-old girl who had been attending the clinic for dry eyes. Six days later she developed adenovirus infection of the eye. Two other members of her family—a 2¼-year-old boy and his mother—contracted the infection nine and 21 days respectively from the onset of her conjunctivitis. Adeno 19 was isolated from the eyes of the doctor and three members of this family. Four other patients apparently contracted the infection from this doctor, but the culture tests on these patients were negative.

INCUBATION PERIOD

In the hospital outbreak the incubation period ranged between four and 12 days with a mean of eight.

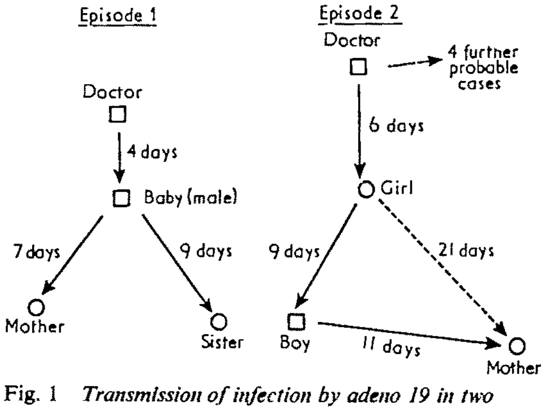

Fig. 1 *Transmission of infection by adeno 19 in two episodes of hospital cross-infection*

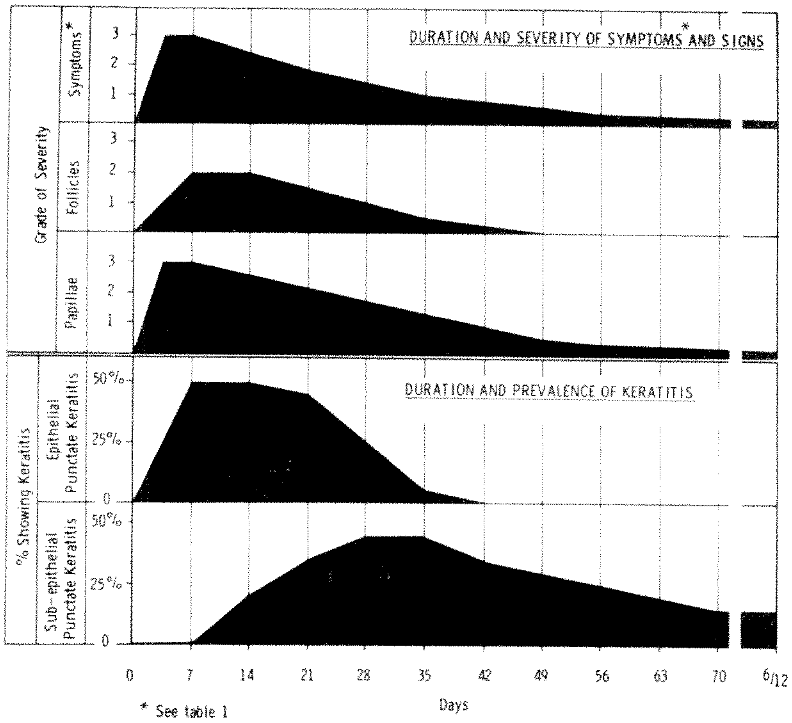

Fig. 2 *Duration and severity of symptoms and signs of disease in 21 cases of adeno 19 keratoconjunctivitis*

SYSTEMIC INFECTION

Four of the 21 patients had rhinitis and sore throats for one week before the conjunctivitis, and one complained of general malaise.

LYMPHADENOPATHY

Three of the 21 patients had enlarged preauricular nodes at the first visit. In two patients this was unilateral and lasted only one week. In the third patient bilateral preauricular adenopathy persisted for two weeks. No glands were visibly enlarged, and no submandibular or cervical lymphadenopathy was observed.

SYMPTOMS

All patients complained of moderate to severe lachrymation, discharge, swelling, inflammation, and a sensation of the presence of a foreign body in the affected eye during the early stage of the infection (Table 1, Fig. 2).

Symptoms were milder in the younger children and in patients who first attended more than 10 days after the onset of symptoms.

SIGNS

In 10 of the 21 cases the second eye became inflamed within four days of the onset of the infection. This occurred between the fifth and tenth day in a further six cases. Five remained unilateral. The average duration of conjunctival inflammation was six weeks (range three to 16 months).

The bulbar conjunctiva showed moderate to severe hyperaemia in 14 and mild to moderate chemosis in 10 patients, with ecchymosis in six.

The prevalence and severity of clinical signs in the palpebral conjunctiva are shown in Table 2 and Fig. 2. At the first attendance all the patients except two who first attended during the resolving stage of their infection showed moderate to severe hyperaemia and diffuse infiltration with papillary and follicular reactions.

Papillary reaction was most severe in the upper tarsal conjunctiva (Figs. 3 and 4). It persisted for

Table 1 *Prevalence and severity of symptoms at first visit in 21 cases of adeno 19 keratoconjunctivitis*

Symptoms	*Severity*		
	Mild	*Moderate*	*Severe*
Lachrymation	5	10	6
Discharge	5	5	6
Swelling of the lids	5	6	4
Redness	5	10	5
Itching	5	2	1
Grittiness	9	5	0
Pain	3	1	1
Photophobia	7	3	1
Blurred vision	6	2	0

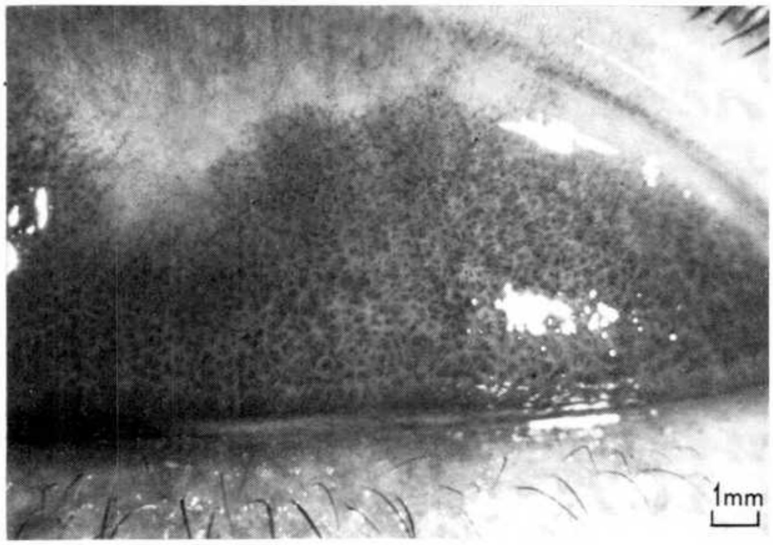

Fig. 3 *Severe papillary reaction in upper tarsal conjunctiva partially obscured by early pseudomembrane in the first week of type 19 adenovirus conjunctivitis* (× 6)

about six weeks in 18 patients, three months in two, and for 16 months in one (Fig. 2).

Table 2 *Prevalence and severity of signs in the palpebral conjunctiva at first visit in 21 cases of adeno 19 keratoconjunctivitis*

Signs	*Severity*		
	Mild	*Moderate*	*Severe*
Hyperaemia	2	11	8
Diffuse infiltration	3	15	3
Papillary hypertrophy	0	8	13
Follicular hypertrophy	4	12	5
Pseudomembrane	3	6	0
Scar	2	2	0

Moderate follicular reaction was present, mainly in the upper and lower fornices, in all 21 patients (Figs. 5, 6, and 7). The follicles were rather small, discrete and lasted three to seven weeks (Fig. 2).

Pseudomembrane (Figs. 8, 9, and 10) was observed in nine of the patients with severe conjunctivitis. It developed seven to 10 days after the onset of infection and lasted one to two weeks. Mild or moderate linear or diffuse scarring (Figs. 11, 12, and 13) of the conjunctiva developed 20 to 30 days from the onset of the infection in four patients who had had rather well marked pseudomembrane.

One patient was of particular interest. In July 1973 a girl of 24 developed an acute bilateral

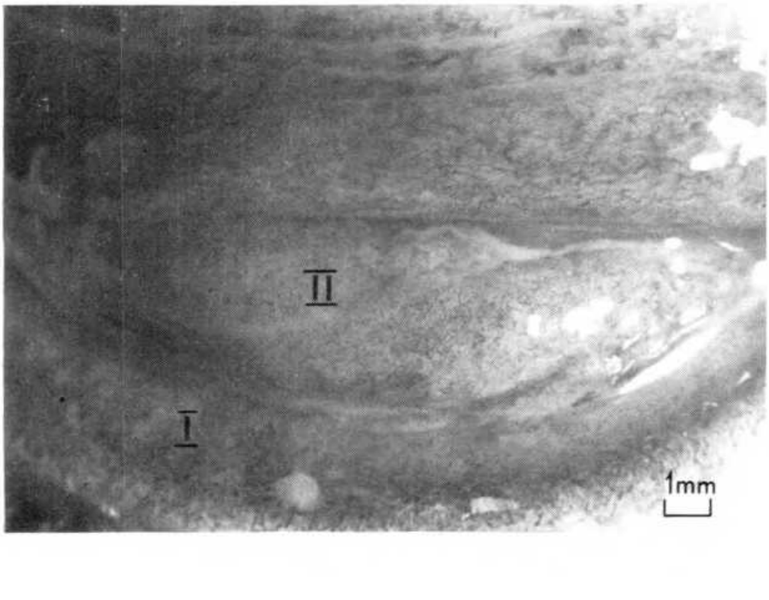

Fig. 4 *Papillary hyperplasia in lower lid conjunctiva:* (*I*) *tarsal,* (*II*) *fornix*

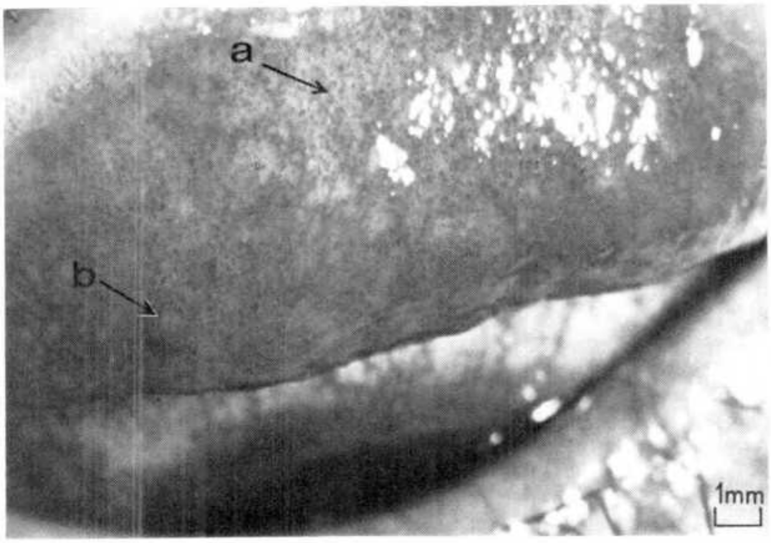

Fig. 5. *Mixed papillary* (a) *and follicular reaction* (b) *in upper tarsal conjunctiva in the second week of type 19 adenovirus conjunctivitis*

keratoconjunctivitis of six weeks' duration. After this she suffered from chronic conjunctivitis with several recrudescences of acute inflammation in one or other eye. She was found to have a bilateral chronic papillary conjunctivitis, most marked in the upper tarsal area, and her cornea were clear. Adeno 19 was isolated from the conjunctiva, when she was referred for investigation, 12 months after the onset of her infection. The condition persisted for a further four months. But after a course of topical treatment with 1% trifluorothymidine (TFT) eye-drops the patient was relieved of symptoms, and the signs of conjunctival inflammation disappeared.

KERATITIS

Of the 21 patients 15 developed keratitis. Moderate to severe fine epithelial punctate keratitis (Jones, 1962) was observed in 10 patients, mainly three to four days from the onset of the conjunctivitis and lasting for one to four weeks. Coarse epithelial punctate keratitis (Jones, 1962) was observed in nine patients, generally in association with fine epithelial punctate keratitis. Thirteen patients

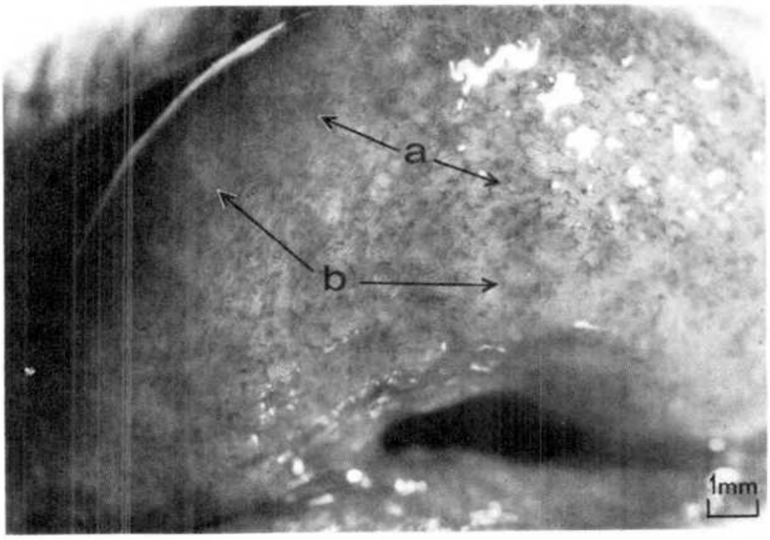

Fig. 6 *Mixed papillary* (a) *and follicular reaction* (b) *in upper fornix conjunctiva in the second week of type 19 adenovirus conjunctivitis*

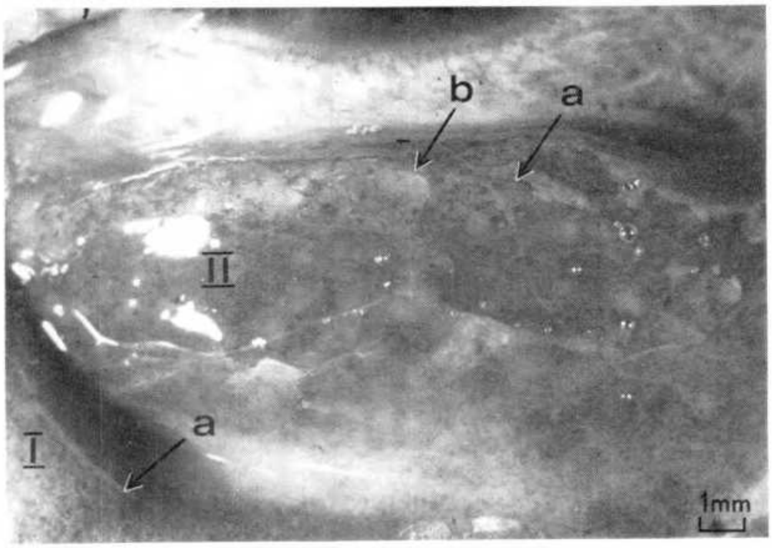

Fig. 7 *Mixed papillary* (a) *and follicular reaction* (b) *with oedema and exudate in the lower lid conjunctiva in* (I) *tarsal and* (II) *fornix areas during the second week of type 19 adenovirus conjunctivitis*

developed moderate to severe subepithelial punctate keratitis (Jones, 1962); most of these opacities were coarse in nature and visible with the naked eye (Fig. 14). Nearly half of these patients showed more than 15 to 20 lesions in the cornea, mainly within the interpalpebral fissure. The average time from onset of symptoms to the occurrence of subepithelial lesions was 17 days (10 to 35 days). The subepithelial keratitis persisted in the majority of these cases longer than a year.

DIFFERENTIAL CYTOLOGY

Conjunctival impressions taken in the early stage of keratoconjunctivitis showed a predominantly mononuclear cell exudate in two-thirds of the patients. In the remaining third there was a mixed mononuclear and polymorphonuclear cell response.

ISOLATION OF VIRUS

Adeno 19 was isolated in HEK cells from each of the 21 cases, with CPE appearing three to 19 days after inoculation. The interval between onset of the disease and collection of conjunctival specimens was less than one week in nine cases, one to two weeks in six cases, three to four weeks in five cases, and in one case it was 12 months.

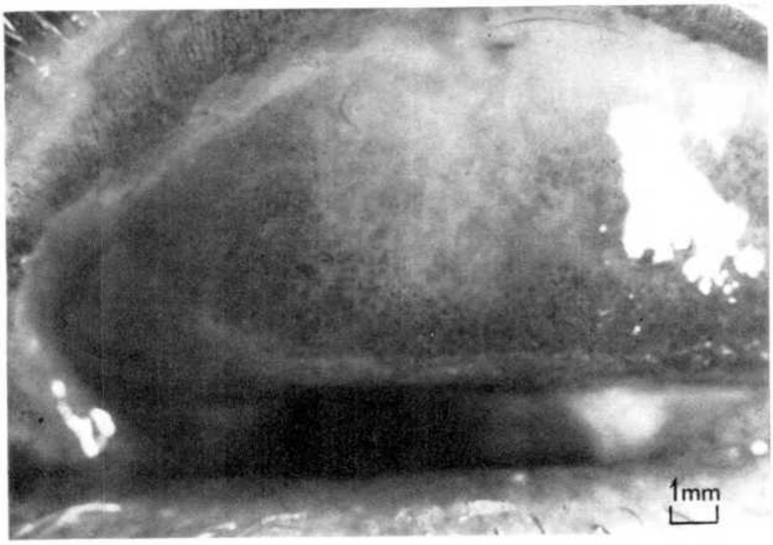

Fig. 8 *Pseudomembrane in upper tarsal conjunctiva in the second week of type 19 adenovirus conjunctivitis*

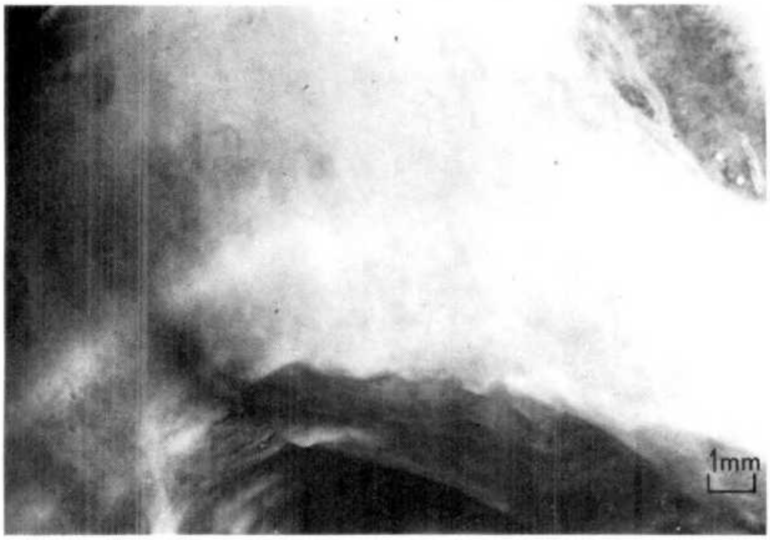

Fig. 9 *Severe pseudomembrane in upper fornix area of conjunctiva in the second week of infection*

Aliquots of the conjunctival specimens collected from nine patients were inoculated on to HEp2 cells in parallel with HEK cells. All the cultures were positive for adeno 19 in both systems, but in HEp2 cells the CPE appeared approximately 10 days later than in HEK cells.

COMPLEMENT FIXATION TEST

Paired or triplicate sera were tested in 15 patients. A minimum four-fold rise in titre was shown in eight patients. A high titre of 1/80 to 1/160 was obtained in six cases.

TREATMENT

While the aetiology was being determined, all patients were initially treated with eye drops or eye ointment of either chloramphenicol or neomycin to prevent secondary bacterial infection.

In nine patients with a mild or moderate keratoconjunctivitis treatment was continued with the antibiotics. The symptoms in these patients disappeared in two to four weeks, and the average course of the disease was approximately six weeks. The other 12 cases who were suffering from a more severe keratoconjunctivitis and had not benefited

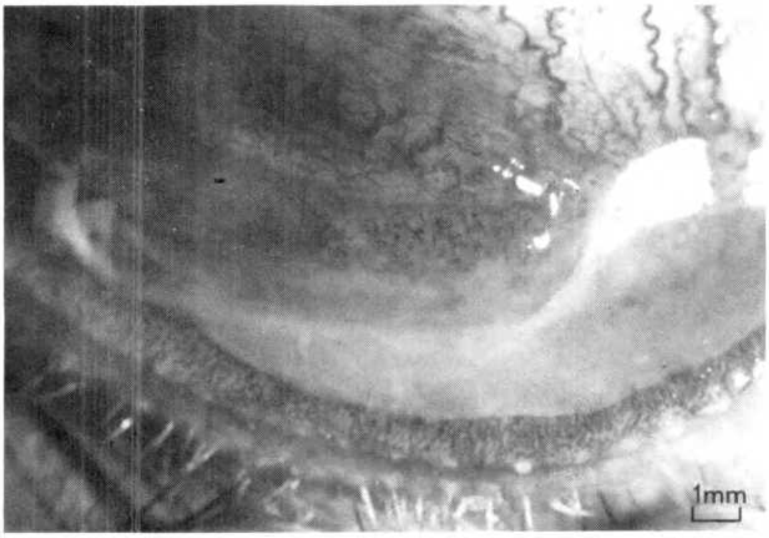

Fig. 10 *Pseudomembrane almost covering lower lid conjunctiva in the second week of infection*

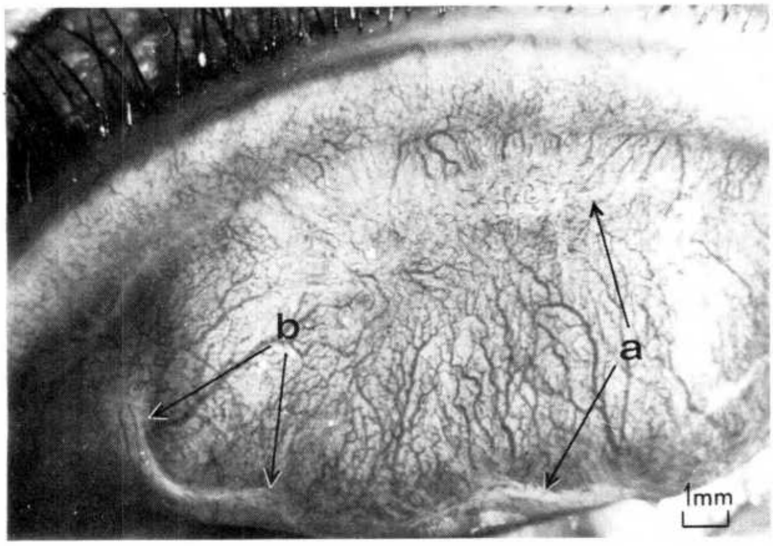

Fig. 11 *Linear* (a) *and synechial scar* (b) *in upper tarsal conjunctiva four weeks after infection*

from the antibiotic therapy were treated with a seven-day course of 1% trifluorothymidine eye-drops (TFT) hourly for the first day, two-hourly for the second day, and five times a day for the next five days. In this group of patients symptoms reduced in less than one to two days and had completely disappeared in two to four days. The range of duration of keratoconjunctivitis in this group of patients was three to four weeks.

Discussion

Keratoconjunctivitis due to adeno types 2, 3, 4, 5, 7, 8, 11, 13, 14, and 15 has been identified in London. Of these, adeno 3 and 7 have been the most common types (Jones, 1962). Type 8 was generally associated with minor hospital outbreaks (Darougar, Gray, Gibson, McSwiggan, and Jones, in preparation).

Although adeno 19 was isolated in 1955 from the inflamed eye of a child with trachoma in Saudi Arabia, it was not reported again as a pathogen until 1973. Since the summer of 1973 sporadic cases and outbreaks of adeno 19 keratoconjunctivitis were seen simultaneously in the USA, Holland, Belgium, Canada, and Scotland (Hierholzer *et al.*, 1974; Vas *et al.*, 1974; Desmyter *et al.*, 1974; Bell and

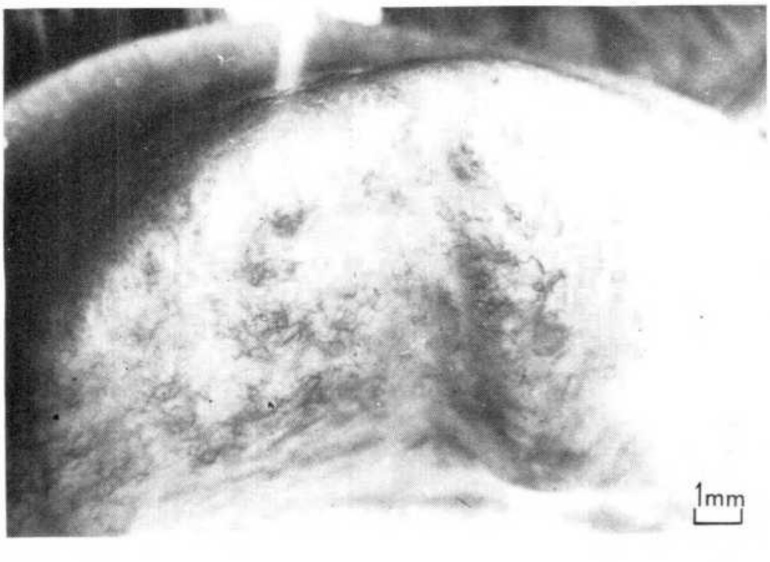

Fig. 12 *Severe diffuse scarring in upper fornix conjunctiva following a severe pseudomembrane (fourth week)*

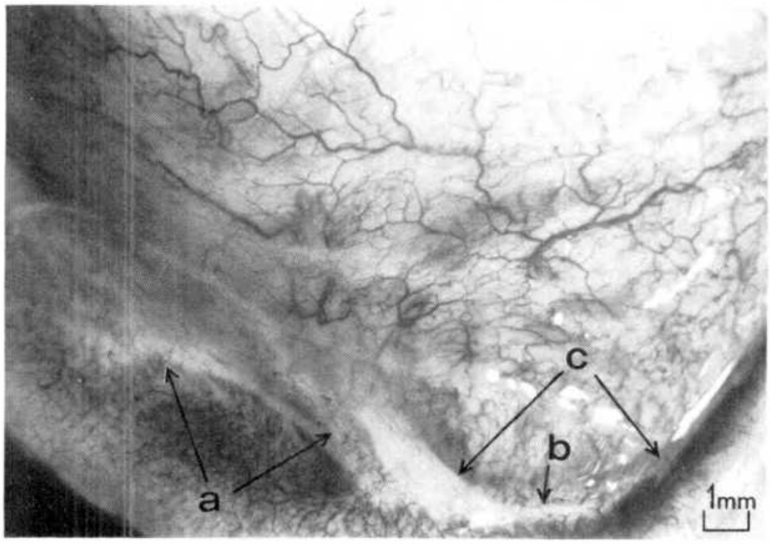

Fig. 13 *Diffuse* (a), *linear* (b), *and severe synechial scarring* (c) *in lower lid conjunctiva* (*fourth week*) *with deformity of the lid*

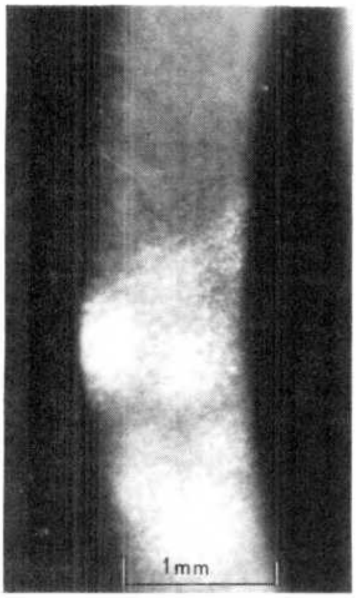

Fig. 14 *Macrophotograph* (× 20) *of confluent coarse subepithelial punctate corneal opacities in the broad slit-lamp beam* (Photograph by N. Brown)

Winton, 1975). The first proved case of adeno 19 keratoconjunctivitis in London was observed in June 1973; more cases were identified in the latter part of 1973 and in 1974, but there was no obvious seasonal variation in incidence of acute keratoconjunctivitis presenting in our clinic, nor was there any evidence of major community outbreaks in London during this period.

The simultaneous occurrence of adeno 19 keratoconjunctivitis in several different countries after the 18-year interval since the original isolation in Saudi Arabia has not been satisfactorily explained. It may have been due to the emergence of a pathogenic variant or to the arrival of the agent in areas in which the resulting disease would come under intensive study (Desmyter *et al.*, 1974).

The clinical features of adeno 19 keratoconjunctivitis—a severe follicular conjunctivitis, sometimes with pseudomembrane and scarring, and commonly with a major subepithelial punctate keratitis but with little in the way of systemic disease—are all closely similar to those of epidemic keratoconjunctivitis caused by adeno 8 (Jawetz *et al.*, 1955; Jones, 1962; Dawson *et al.*, 1970; Hart *et al.*, 1972). The ability of both agents to cause hospital outbreaks (Hierholzer *et al.*, 1974; Vas *et al.*, 1974) greatly accentuates this similarity and makes it clear that adeno 19 can cause epidemic keratoconjunctivitis.

The case of recurrent chronic papillary conjunctivitis that persisted for 16 months after an acute onset indicates the probable way in which iatrogenic hospital- or clinic-based outbreaks of eye-to-eye transmission of infection with adeno 19 may arise. It is noteworthy that infective virus was being shed from the patient's eyes after 12 months of recrudescent or recurrent illness, the clinical features of which were entirely different from those of the classical case of acute follicular adenovirus eye infection with recovery within four to six weeks. Such a patient presenting to an ophthalmologist would hitherto not have aroused the suspicion of adenovirus infection, for even those trained especially in external eye diseases would have dismissed the possibility of adenovirus infection being responsible for chronic papillary conjunctivitis of this nature.

It is easy to see how such a patient, with a rather nondescript illness, which in this case was referred as a probable case of conjunctivitis artefacta, would have a number of investigations carried out, including lachrymal syringing, and would not be segregated from other patients or be handled with particular care to prevent cross-infection. Such a case would therefore be especially likely to remain unrecognised and to supply the source of virus for a new outbreak of epidemic keratoconjunctivitis. It is therefore of importance that chronic or recurrent cases of papillary conjunctivitis should rouse the suspicion of adenovirus infection and should be appropriately investigated.

It is of interest that in this case the signs and symptoms of disease rapidly resolved, and eye cultures became negative for adenovirus on treatment with 1% TFT eye-drops hourly for the first day, two-hourly for the second day, and five times daily for the next five days. We had a clinical impression that this treatment also benefited and shortened the duration of illness in 12 cases in the present outbreak in which symptoms were severe and persistent. This is in contrast with the apparent ineffectiveness of 1% TFT drops in the ordinary run of sporadic adenovirus eye infection due to types other than 19 (Darougar, Hunter, Gibson, and Jones, in preparation).

While the number of specimens inoculated into HEp2 cells in this study was small, it appears that the sensitivity of this cell line is similar to that of HEK cells for the isolation of adeno 19, although the development of CPE was markedly slower. Other cell cultures, including primary human thyroid cells, human amnion cells, and primary African green monkey kidney cells, have also been satisfactory for the isolation of adeno 19 (Desmyter *et al.*, 1974; Bell and Winton, 1975).

The authors are indebted to colleagues at Moorfields Eye Hospital for referring patients, to members of the External Eye Disease Clinic, Moorfields Eye Hospital, for the collection of clinical specimens, to Mr T. Tarrant for the graphics, and to the audiovisual department of the Institute of Ophthalmology for help in preparation of photographs. This work was supported by a locally organised clinical research grant, Moorfields Eye Hospital, City Road.

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A case report of fowl plague keratoconjunctivitis

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SUMMARY A case of human fowl plague keratoconjunctivitis occurred after accidental laboratory exposure. The conjunctivitis was characterised by follicle formation and a mucopurulent discharge, and ran a self-limiting course over two weeks. The keratitis was of an unusual type and consisted of small intraepithelial opacities, which appeared after one week and resolved completely over the next three weeks. The infection, confirmed by viral culture, was produced by Dutch strain (Hav 1 Neq 1) of fowl plague virus.

Fowl plague is an acute, highly infectious, generally fatal viral infection of fowls. The virus is one of the avian influenza viruses which form part of the orthomyxovirus group. Fowl plague had not been described in Australia when an outbreak occurred on two chicken and one duck properties at Keysborough, Victoria, in January 1976 (Turner, 1976). The isolation of fowl plague virus (FPV) from man has been reported on only one previous occasion (De Lay *et al.*, 1967). This paper reports a confirmed accidental laboratory infection occurring in a human.

Case report

The patient, a 24-year-old female laboratory technican in good health, splashed allantoic fluids containing FPV on the right side of her face. The accident occurred while opening the tops of infected eggs to harvest allantoic fluids within a biohazard unit, when an egg shattered on handling. At the time the patient believed fluids had come in contact only with the skin, but the face and eye on the right side were washed immediately with water.

Twenty-six hours after the accident the patient noted a foreign body sensation in the right eye, and three hours later a yellow discharge was present, more noticeable under the upper lid. Twelve hours later she reported to her local doctor, who, after taking swabs for culture, prescribed chloramphenicol drops. Over the next 24 hours the right eyelids became more swollen, and the discharge continued until she presented to the casualty section of the Royal Victorian Eye and Ear Hospital. This was 65 hours after exposure and 39 hours after the onset of symptoms.

On examination she had moderate oedema of the right eyelids and enlarged right preauricular lymph nodes. There was a follicular conjunctivitis with 2 to 3 mm follicles in the tarsal and fornix conjunctiva, and a mucopurulent discharge. The cornea was clear and bright with no epithelial change and normal sensation. The anterior chamber showed no activity. Examination of her left eye was normal. She was otherwise in good health. The chloramphenicol drops were stopped, and 'Zincfrin' drops and saline bathing commenced four times a day.

Twenty-four hours later there was a marked symptomatic improvement and a reduction in the oedema and discharge. Six days later there was a mild residual conjunctival injection and a few small follicles remaining in the fornix. Thirteen small intraepithelial opacities, white-grey in colour, were observed deep in the epithelium (Figs. 1 and 2). These opacities did not involve Bowman's membranes, alter the contour of the overlying epithelium, or stain with Bengal rose or fluorescein. No changes were observed in the anterior chamber. The preauricular nodes were no longer palpable or tender, and the eye felt comfortable. Seven days later, 16 days after exposure, a very faint haze remained in the area of the corneal opacities. The residual conjunctival injection and follicles had cleared. This

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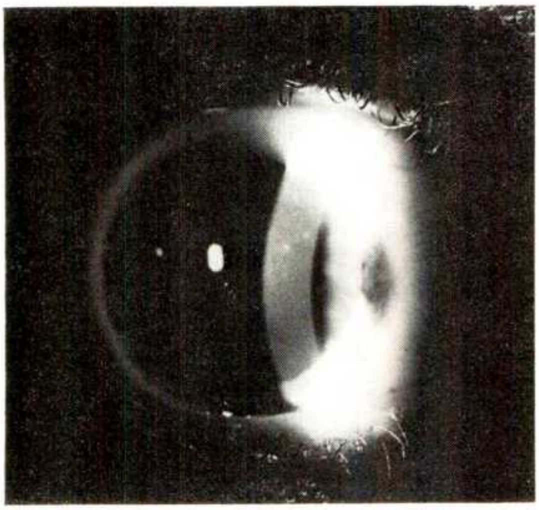

Fig. 1 *Clinical photograph taken on day 9 showing several of the intraepithelial corneal opacities*

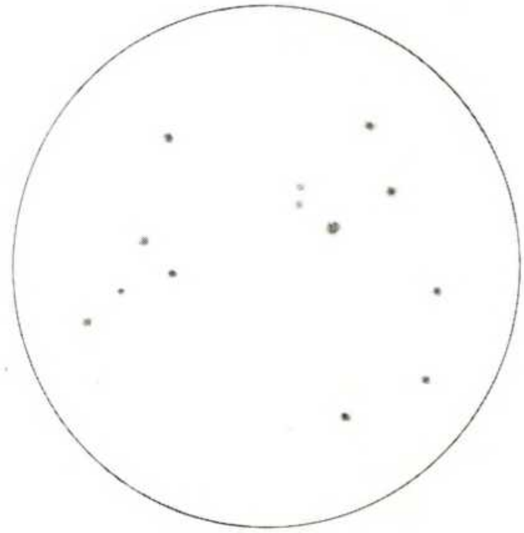

Fig. 2 *Drawing showing the distribution of corneal opacities seen on day 9*

intraepithelial haze had disappeared in a further seven days, and the ocular examination was entirely normal.

Investigations

Swabs were collected separately from the medial and lateral canthus and upper and lower lids of the affected eye, and placed into 3 ml brain heart infusion broth, containing 10 000 units of penicillin and 10 000 μg of streptomycin per ml. The samples were returned to the laboratory, and 0·1 ml of sample fluid was inoculated in each of four 10-day-old chicken embryos by the allantoic route. The haemagglutinins in allantoic fluids were identified by the β-procedure of the haemagglutination—inhibition test using reference fowl plague antiserum and virus (Expert Committee on Respiratory Virus Diseases).

All eggs inoculated with the four samples were dead at 40 hours after inoculation, and allantoic fluids contained haemagglutinins for chicken erythrocytes. These haemagglutinins were identified as FPV by the haemagglutination-inhibition test.

Blood samples were taken on 9, 16, and 25 days after exposure. Serum was tested against 4 units of fowl plague haemagglutinin on the haemagglutination-inhibition test (Expert Committee on Respiratory Virus Diseases, 1959). The samples, taken at days 9, 16, and 25, had titres of 1 in 8, 1 in 16, and 1 in 8, respectively, when tested for haemagglutination-inhibition antibody.

Discussion

The patient presented with a typical viral follicular conjunctivitis 26 hours after accidental exposure to FPV. The conjunctivitis had almost run its course when, on the eighth day of the illness, an asymptomatic intraepithelial keratitis was noted. These opacities had cleared within three weeks. The keratitis differed from that seen in other viral infections, such as adenovirus types 3 or 8 or Newcastle disease (Hales, 1973) in that it was asymptomatic, non-staining, and the opacities were situated entirely in the deeper epithelial layers.

FPV was isolated from the conjunctival sac, but a significant four-fold rise in haemagglutination-inhibition titre to FPV was not demonstrated. The first blood sample, however, was not taken until nine days after exposure. The serum titre before or at the time of exposure is unknown, and the titre may have risen before the first sampling. Serum antibody can be detected by day 9 in inoculated chickens, but the titre usually continues to rise until about day 20. However, acute systemic disease is observed in chickens for a much longer period than eight days.

Human infection with FPV has not been well documented in the past, although FPV can be grown in human cell cultures (Chaproniere and Pereira, 1955). The strain of FPV causing an outbreak of disease in chickens in Victoria in 1976 was Dutch strain, which is antigenically Hav 1 Neq 1 (Turner, 1976). Strains of FPV which have been isolated from outbreaks in fowls in other parts of the world have different neuraminidase antigens (Tumova and Schild, 1972). Isolation of Dutch strain of FPV has been previously recorded only from an outbreak in Indonesia in 1927. Human susceptibility to FPV may be dependent on virus strain and individual variability.

The patient reported by De Lay *et al.* (1967) was suffering from an undiagnosed illness after visiting the Far East and Middle East areas, where fowl plague is enzootic. The virus was cultured from a blood sample. Further study on the isolated virus demonstrated that it was very closely related, if not identical, to FPV (Campbell *et al.*, 1970). However, the incubation time was thought to be 30 days, much longer than that for birds (usually four hours to two days) and no serum antibody was detected.

Fowl plague is characterised in fowls by a viraemia producing oedema, congestion, petechial haemorrhages, and focal areas of necrosis. These changes are seen particularly in the skin, respiratory and enteric tracts, and the nervous system. The ocular involvement consists of a reddened and swollen conjunctiva and periorbital oedema (Stubbs, 1965). It is interesting that this case showed considerable lid oedema, but no petechiae were noted.

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Management of keratoplasty in the early stages

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SUMMARY Frequent, if not daily, slit-lamp examination of the patient with a penetrating transplant is indicated for more than one reason: it will lead to the early detection of any defect of the host-graft junction or of the graft's posterior surface; it will permit an early diagnosis of the peripheral cornea-iris touch syndrome with all its potential consequences (acute, irreversible mydriasis, iris atrophy, and now and then secondary glaucoma); it will give an exact clue to when to remove the continuous sutures long after these have been covered by epithelium; and it will alert the surgeon in the event of a localised infection. Early and late opacification of the graft will also be correctly appraised, so that the surgeon will know when to wait and when to take the appropriate action.

Despite the development of new methods for the preservation of corneal donor material, in most centres where corneal transplantation is performed routinely fresh material is preferred. The donor eyes are removed less than six hours after death and are stored in a moist chamber at 4°C for a maximum of 24 hours. As a rule only material from donors aged 50 years or less is used so as to make sure that the grafted endothelium will be of optimal viability.

Failures due to damage inflicted to initially good material have become rare since proper microsurgical techniques and tools have been used. The main causes of failure that remain are, first, those inherent in some conditions in which surgery has a guarded prognosis, and, secondly, several complications whose appearance seems unrelated to the quality of the transplanted disc, to the instrumentation employed, or to the surgeon's dexterity.

This paper is not intended to be a list of the pitfalls encountered during or after the performance of partial penetrating keratoplasty, as this would be futile. Its aim is to study some early prognostic signs as they become apparent in the postoperative course so that adequate and timely treatment may be instituted.

Graft defects

A point which has never been stressed sufficiently is that even in the case of an avascular and uninfected host cornea, the impeccable transplantation of healthy tissue which has been carefully examined preoperatively may not always result at once in a crystal-clear graft, or in a graft that can be considered wholly satisfactory. While some of the deficiencies detected early after the operation require no treatment and will mend spontaneously, others are a bad omen and require that immediate measures be taken if success is to be attained.

A crinkled posterior surface of the graft is a frequent finding after penetrating keratoplasty. Owing to the presence of folds in Descemet's membrane it may be caused either by stromal oedema or by an uneven tension of the direct or running monofilament sutures which keep the graft in place. If the donor cornea is waterlogged when the graft is cut, the imbibition tends to disappear once the graft is accurately applied. Initially increased, the corneal thickness will return to normal in a few days' time. When the wrinkles in Descemet's membrane result from uneven traction, they will persist until the sutures are removed and will not be accompanied by an increased graft thickness.

If a single or double continuous suture is used, either alone or in combination with a number of border-to-border sutures, apposition of the wound edges is good. Because of the very fact that the edges are fitted together quite closely, some marginal epithelial oedema develops and may remain visible for weeks. The trouble with this is that it will cause an irregularity of the corneal reflex, as may be seen with a keratoscopic disc, and render any ophthalmometric reading useless or grossly lacking in precision.

There are cases in which the graft is clear when it is placed in position only to become oedematous later. This may occur even if proper suturing has been done. An opalescence, slight at first, may

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subsequently take on the appearance of a striate keratitis, which indicates unequivocally that the endothelium is suffering or, more rarely, that there is a defective alignment between the graft and the host, so that the aqueous seeps into the stroma. Not uncommonly some degree of epithelial oedema is seen in large parts of the graft. The degree of the opacity which may develop in the graft after surgery varies. It may be very faint, merely a slight haze, discernible only with retroillumination, or it may be rather dense. It may affect the entire cornea or only a sector. And it may lie in the endothelium, the stroma, or the epithelium. Such an appearance causes grave concern to the surgeon although it may produce no permanent damage and vanish without trace in a couple of weeks. The grafted cornea then regains its normal thickness unless endothelial disease existed in the donor cornea.

In those cases in which the cornea is still imperfectly transparent at the end of two weeks a sub-Tenon's injection of a slow-resorption steroid is indicated. This may be done as an office procedure after the removal of the direct sutures. Far from retarding endothelial recovery (Sánchez and Polack, 1974), the administration of topical steroids even in large doses seems to have a highly beneficial effect in any situation where the endothelium is less than perfectly healthy. But if the graft does not clear in a very few more days it must be replaced, as the chances of its becoming clear again are slim (Barraquer and Rutllán, 1969).

When oedema and opacification of the graft become manifest at about the third postoperative week, the conclusion should be that one is faced with an allograft reaction, a problem which falls beyond the scope of this paper. In this respect let us only say that rejection may be preceded by an increased graft thickness, which becomes apparent before the development of any loss in transparency when serial measurements with the Haag-Streit pachometer are made. Another early sign of rejection is represented by the deposition of a number of small grey precipitates on the posterior surface of the graft.

Both in the case of the early opacification due to the poor quality of the donor material and in that of an incipient true allograft reaction, direct examination of the endothelium with a specular reflection microscope may provide valuable information and alert the surgeon as to a possibly unfavourable course.

Sudden mydriasis

In those cases of keratoconus where the air bubble injected at the end of the procedure happens to escape from the eye—an accident which takes place occasionally even when the sutures have been applied accurately and a precise fit has been achieved—the anterior chamber may be shallow at the first dressing and remain so for a day or two. Likewise, resorption of air without the formation of an equivalent amount of aqueous will result in a partially flat chamber. In patients submitted to penetrating keratoplasty for conditions other than keratoconus the anterior chamber may have been of little depth before surgery, particularly after the age of 50, in which case it will tend to become still shallower postoperatively owing to the flattening effect which the operation frequently exerts on the recipient cornea. This effect may become apparent only after the air which has been injected is resorbed.

If the pupil remains small, nothing untoward will happen. If, on the other hand, a sudden mydriasis develops, for example after the instillation of atropine, the ciliary part of the iris will come dangerously close to the posterior surface of the host cornea and at some point make contact with it (Fig. 1). This cornea-iris touch, which does not seem to have attracted much attention, is nothing short of disastrous, as it will perpetuate the mydriasis and trigger the development of a diffuse atrophy of the mesenchymal iris layers. That this is not caused by pupillary block is shown by the fact that after cataract extraction, where blocking of the pupillary opening through herniation of the hyaloid-contained vitreous is not rare and may be unrelieved for many hours, the above features are never observed as part of the regular picture. Pupillary dilatation, which eases pupillary block, is precisely what in most cases launches the whole cycle of events (Urrets-Zavalía, 1965).

Consequently, such contact should be broken

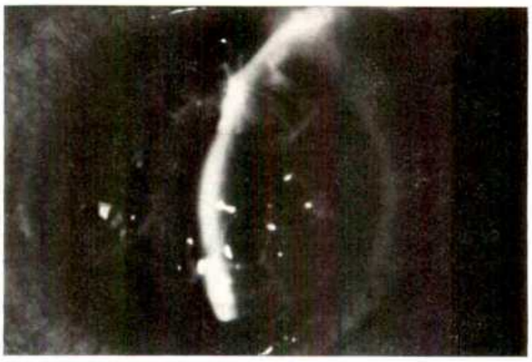

Fig. 1 *Partial penetrating keratoplasty for keratoconus. Large, irregular mydriasis appeared after marginal cornea-iris touch developed between the 12 o'clock and the 3 o'clock meridians*

These scores were modified according to the density of the corneal lesion as follows: Nothing was added to the score if the lesion was nebulous, 1+ was added if it was macular, and 2+ was added if it was leukomatous. In this way the final score ranged from 0 to 5+.

After instilling a drop of anaesthetic in both eyes of each animal, we gave the animals in each group a single daily subconjunctival injection, as follows:

Group 1: Ticarcillin, 2·5 mg (0·2 ml of a 12·5 mg/ml solution);
Group 2: Gentamicin, 1·6 mg (0·2 ml of an 8·0 mg/ml solution);
Group 3: Ticarcillin ,1·2 mg (0·1 ml of a 12·5 mg/ml solution) combined with gentamicin, 0·8 mg (0·1 ml of an 8·0 mg/ml solution);
Group 4: Saline solution, 0·2 ml.

These doses were selected on the basis of an earlier pilot study in which we found that pseudomonas could not be recovered after three days of treatment with ticarcillin in doses of 10, 40, or 160 mg, but could be recovered after doses of 2·5 and 5·0 mg; and that the organism could not be recovered after three days of treatment with gentamicin in doses of 3·2 and 6·4 mg, but could be recovered after doses of 0·1, 0·4, and 1·6 mg. Since we needed at least minimal growth of the organism in order to compare the results of using each antibiotic alone with using the two in combination, we gave the doses listed (ticarcillin 2·5 mg, and gentamicin 1·6 mg).

The animals were given these injections and their lesions were graded for three days. On day 4 no treatment was given and all of the animals were killed. All of the corneas were removed, ground separately, and cultured on Mueller-Hinton plates. The colonies of pseudomonas on the plates were then counted.

TOXICITY

We tested the toxicity of ticarcillin by injecting both eyes of the four remaining (uninfected) rabbits with 10, 25, 50, and 100 mg of ticarcillin subconjunctivally. Each rabbit received one of these doses in both eyes daily for three consecutive days. For two weeks the rabbits' conjunctivas and corneas were examined daily for any adverse effects.

Results

IN-VITRO TESTING

The minimal inhibitory concentrations (MIC) of the three drugs tested were as follows: Ticarcillin, 50 μg/ml, carbenicillin, 100 μg/ml; and gentamicin, 0·2 μg/ml. The minimal bactericidal concentrations (MBC) were as follows: Ticarcillin, 100 μg/ml; carbenicillin, 200 μg/ml; and gentamicin, 0·2 μg/ml.

In Fig. 1 we show the growth curves of the organism in the presence of ticarcillin, gentamicin, combined ticarcillin and gentamicin, and when no antibiotic was used. In these growth studies the concentrations of the antibiotics were lower than their MICs. In the control group and gentamicin group the growth curves were the same. In the ticarcillin group there was a 1000-fold reduction in the number of viable organisms after 24 hours, and in the combined ticarcillin and gentamicin group there was a 100-fold greater reduction in this number after 24 hours.

IN-VIVO TESTING

Table 1 shows the results of the clinical scoring of the experimental keratitis on four successive days. In order to compare the severity of the keratitis in the four treatment groups the number of eyes with the same score in each group on day 4 were added together (Table 2). To make a statistical comparison of the results, we divided the keratitis into two categories: Mild for scores 0 to 2, and severe for scores 3 to 5. The data were then subjected to Fisher's exact probability test.

There were significant differences between the groups treated with either ticarcillin alone or gentamicin alone and the group treated with saline solution ($P < 0·05$), and a greater difference between the group treated with ticarcillin and gentamicin combined and the group treated with saline solution ($P < 0·01$). There were also significant differences between the groups treated with ticarcillin alone or gentamicin alone and the group treated with the drugs in combination ($P < 0·05$). Only between the

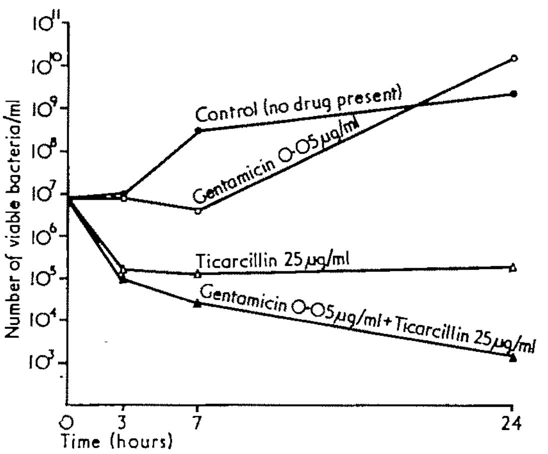

Fig. 1 *Growth curves of pseudomonas in presence of ticarcillin, gentamicin, combined ticarcillin and gentamicin, and when no antibiotic was used*

Table 1 *Clinical evaluation and pseudomonas colony count after treatment of experimental pseudomonas keratitis with ticarcillin, gentamicin, combined ticarcillin and gentamicin, and saline solution*

Rabbit No.	*Treatment*	*Clinical scores*								*Pseudomonas Colony count*	
		*Day 1**		*Day 2*		*Day 3*		*Day 4*			
		RE	*LE*	*RE*	*LE*	*RE*	*LE*	*RE*	*LE*	*RE*	*LE*
11	Ticarcillin	2	2	3	3	2	2	2	2	0	5
12		2	2	2	2	2	2	2	2	2	TNTC†
13		2	2	3	3	4	3	4	4	13	45
14		2	2	3	3	4	3	4	4	261	19
15		3	3	3	3	3	3	3	4	7	5
16		2	2	2	2	2	2	2	2	116	13
17		2	2	3	3	3	3	3	3	2	0
18	Gentamicin	2	2	3	2	3	3	3	3	0	5
19		2	2	2	3	2	3	2	3	612	0
20		2	2	1	2	1	2	0	2	0	1
21		2	2	2	2	2	2	2	2	0	1
22		2	2	4	4	5	4	4	4	9	280
23		3	3	3	3	4	4	3	3	1304	TNTC
24		3	3	3	2	3	2	3	2	TNTC	1024
25	Ticarcillin and gentamicin	2	2	3	2	3	2	3	2	65	2
26		2	2	1	1	0	1	0	1	49	0
27		3	2	2	2	2	2	2	2	0	1034
28		2	2	3	2	3	3	3	2	0	0
29		2	2	3	2	3	2	2	2	227	2
30		2	2	2	2	2	2	2	2	12	0
31		2	2	2	3	2	3	2	2	1	22
32	Saline solution	2	2	3	4	4	4	3	3	463	TNTC
33		2	3	4	4	4	4	4	4	1010	TNTC
34		2	2	4	4	4	4	5	4	TNTC	TNTC
35		3	2	4	4	4	3	4	4	TNTC	TNTC
36		2	2	3	3	3	3	3	4	344	TNTC
37		2	2	3	3	3	3	4	3	172	TNTC
38		2	2	2	3	3	4	3	3	0	TNTC

*Postinoculation †Too numerous to count.

groups treated with ticarcillin alone and gentamicin alone was the difference insignificant.

Table 1 also shows the result of pseudomonas colony counts on culture plates prepared at the end of the treatment schedule. (On day 1 after the pseudomonas inoculation—before treatment was started—the organism had been recovered in cultures of corneal material from all of the eyes.)

By Student's *t* test there was a significant difference between the colony counts of the groups treated with ticarcillin, gentamicin, and the two drugs in combination, and the colony count of the group treated with saline solution ($P<0{\cdot}01$); but there was no significant difference by this test among the antibiotic-treated groups, whether treated by one drug alone or by the two combined.

Table 2 *Comparison of clinical scores of 56 rabbit eyes with experimental pseudomonas keratitis on day 4 after beginning of treatment*

Treatment	*No. of eyes treated*	*Clinical scores*					
		0	*1+*	*2+*	*3+*	*4+*	*5+*
Ticarcillin	14	0*	0	6	3	5	0
Gentamicin	14	1	0	5	6	2	0
Ticarcillin and gentamicin	14	1	1	10	2	0	0
Saline solution	14	0	0	0	6	7	1

*Total number of eyes with this score on day 4

TOXICITY

In the rabbits injected with the four different doses of ticarcillin (from 10 to 100 mg) the only noticeable change in the conjunctiva was slight hyperaemia at the site of the injection and an occasional subconjunctival haemorrhage. The cornea remained clear throughout the period of observation. The conjunctival hyperaemia subsided in two days with the lowest dose of ticarcillin, and in seven days with the highest dose. No conjunctival necrosis occurred.

Discussion

On the basis of their respective MICs against the pseudomonas strain used in this *in-vitro* experiment ticarcillin was found to be twice as active as carbenicillin—a difference also noted by other investigators (Bodey and Deerhake, 1971; Mai and Bulow, 1974).

When ticarcillin and gentamicin were combined *in vitro*, there was a 100-fold reduction in the growth of the organism after 24 hours' incubation (Fig. 1). This effect was clearly additive—and possibly synergistic. Penicillin and gentamicin are known to be synergistic when used together against enterococci

(Moellering *et al.*, 1973). The cell-wall inhibitor (penicillin) facilitates the passage of the aminoglycoside (gentamicin) into the cytoplasm of the bacterial cell. Ultimately a lethal concentration is reached and ribosomal protein synthesis is blocked.

In comparing the *in-vivo* results it should be emphasised that the doses we used were lower than the therapeutic doses of these drugs. But even with these low doses there were significant clinical differences between the ticarcillin- and gentamicin-treated groups and the group treated with saline solution. The best results were obtained when the ticarcillin and gentamicin were combined.

The culture plates prepared at the end of the treatment period showed a significant suppression of the growth of the organism in the groups treated with ticarcillin, gentamicin, or the two drugs in combination, in comparison with the group treated with saline solution. Although there was no significant difference in the colony counts between the group treated with the antibiotics in combination and the groups treated with each antibiotic alone, there were fewer colonies in the combination group, and on none of the plates in this group was the growth confluent.

Ticarcillin by itself seems to be a promising antibiotic for the treatment of pseudomonas keratitis in rabbits. The advantage of combining it with gentamicin is that the amount of each antibiotic can then be reduced and the risk of toxicity minimised.

Ticarcillin is readily soluble in water and can be given systemically in doses of up to 20 g/day (Wise and Reeves, 1974). The only adverse effect noted so far is the pain the drug may cause at the injection site when it is given intramuscularly.

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Xeroderma pigmentosum and band-shaped nodular corneal dystrophy

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SUMMARY A case of xeroderma pigmentosum with associated band-shaped nodular dystrophy of the cornea is discussed. Band-shaped nodular dystrophy of the cornea usually occurs in elderly Bantu men. Band-shaped nodular dystrophy in a young Bantu man suffering from a genetically determined solar sensitive disease lends credence to the possibility that band-shaped nodular dystrophy is a solar sensitive disease, as has so often been postulated.

Xeroderma pigmentosum is an inherited progressive precancerous disorder of skin and mucous membranes. The disease was first described by Kaposi in 1874 and is said to be rare in Africans, in whom only 16 cases have been reported involving Bantus (Loewenthal and Trowell, 1938; Targousky and Loewenthal, 1956; Harris and Keet, 1960; Sevel, 1963). Band-shaped nodular dystrophy of the cornea was first described in the Bantu by Etzine and Kaufmann (1964) and further cases were subsequently reported by Freedman (1973).

This paper concerns the occurrence of both xeroderma pigmentosum and band-shaped nodular dystrophy in a 30-year-old Bantu.

Case report

A 30-year-old man (Fig. 1) presented to the St John Eye Hospital, Baragwanath, with the complaint of poor vision since birth (Case 1). On examination, his visual acuity was hand movements at half a metre in both eyes. Unlike other cases of xeroderma pigmentosum he was not markedly photophobic. Both corneas showed diffuse non-vascularised opacities, opacification extending from the epithelium through to superficial stroma. In addition both corneas showed the presence of stage 2 band-shaped nodular dystrophy (Fig. 2). The characteristic juxta-limbal pigmentation as seen in band-shaped nodular dystrophy was also present. No details of the anterior chamber could be seen, and no view of the lenses or fundi was obtainable.

The patient's 13-year-old brother had undergone a corneal transplant for total corneal opacities 2 months earlier (Case 2). A third brother aged 8 years showed some interesting clinical features (Case 3). His left eye had an opaque cornea similar in appearance to the corneas of his 2 brothers (Fig. 3). His right cornea was completely clear, and on this side he had a ptotic lid. All 3 brothers were

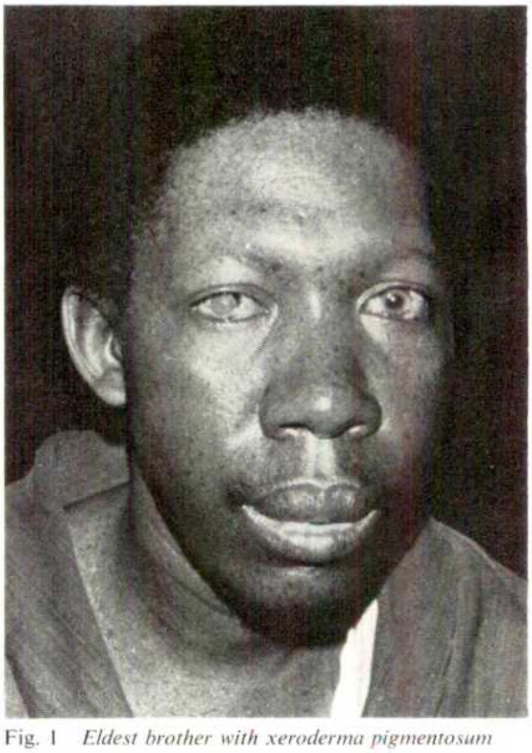

Fig. 1 *Eldest brother with xeroderma pigmentosum*

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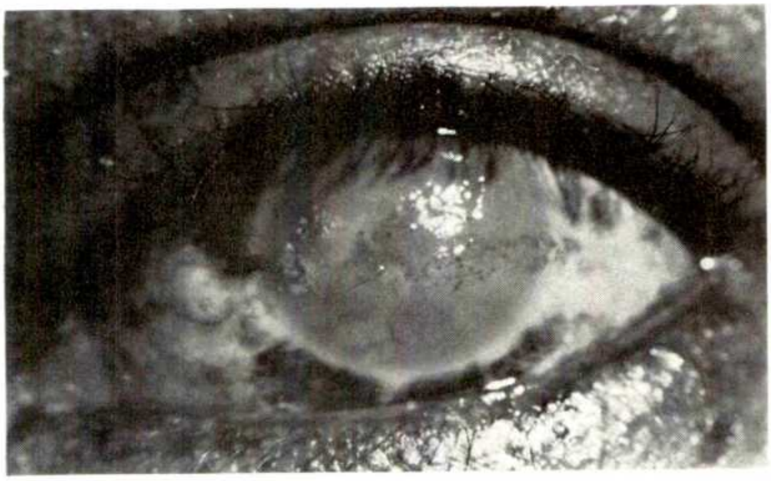

Fig. 2 *Band-shaped nodular dystrophy combined with opacity of cornea due to xeroderma pigmentosum*

found to have xeroderma pigmentosum with the typical skin lesions characterised by multiple, fine hyperpigmented macular lesions of the skin (Figs. 4, 5).

The patient underwent a right-sided penetrating 8 mm keratoplasty. Histological examination of the corneal button showed the changes characteristic of band-shaped nodular dystrophy. Hyaline-like deposits were found to be present in the superficial stroma, with destruction of the basement membrane of the epithelium. Apart from some irregularity of the superficial stroma, the rest of the corneal stroma appeared to be normal. The typical histological changes of xeroderma pigmentosa as seen in other cases, and characterised by irregularity of the superficial corneal stroma, were chiefly masked by the presence of the hyaline deposits (Figs. 6, 7, 8).

Discussion

The case shows some unusual features related to both xeroderma pigmentosum and band-shaped nodular dystrophy. Xeroderma pigmentosum tends to cause ocular symptoms more commonly in Black than in Caucasoid patients, the incidence of ocular involvement being 80% in the former and 30% in the latter (Giller and Kaufmann, 1959), with possible greater susceptibility to ultraviolet rays of ocular and periocular tissues in the Black patients. Certainly the case reported in this study showed relatively

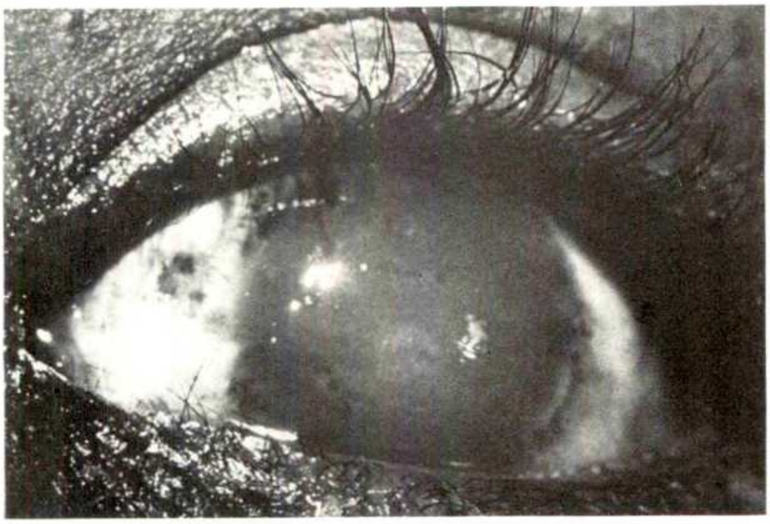

Fig. 3 *Opaque cornea in left eye of youngest brother with xeroderma pigmentosum*

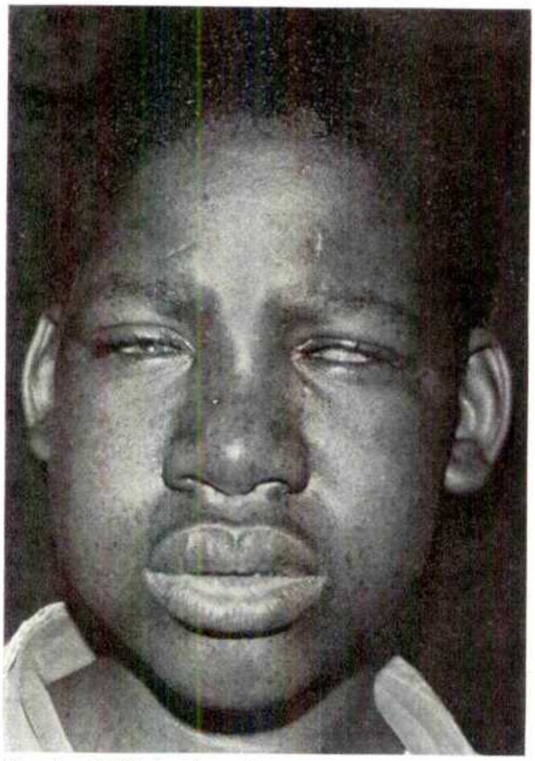

Fig. 4 *Middle brother with xeroderma pigmentosum*

mild skin manifestations of the disease and fairly marked ocular involvement resulting in blindness. The more commonly associated ocular findings of xeroderma characterised by erythema of lid skin, conjunctival erythema with associated purulent discharge, pinguecula, pterygia, and limbal masses were not seen in the case reported. Increased limbal pigmentation of the conjunctiva was noted in this case, as it has been in cases of band-shaped nodular dystrophy. The appearance of a diffuse pannus-like infiltrate of the cornea is a common finding in xeroderma pigmentosum and similar changes have been seen in 3 other Bantu patients with the disease. All 3 patients were related.

Band-shaped nodular dystrophy of the cornea occurring in Bantus was first described by Etzine and Kaufmann (1964). Subsequently a report appeared of the condition in 65 cases of band-shaped nodular dystrophy in the Bantu (Freedman, 1973). The youngest case in that series was 50 years old; thus the patient in this report would appear to be the youngest Bantu to be described with band-shaped nodular dystrophy. The cornea in this patient showed a fairly advanced degree of the condition, being stage 3 out of 5 stages as classified by Freedman (1973). The occurrence of band-shaped nodular dystrophy in conjunction with a disease entity characterised by known susceptibility to actinic rays may lend credence to the theory that band-shaped nodular dystrophy may be aetiologically related to degeneration by actinic rays, as has been suggested. Furthermore, the young age at which this occurred would substantiate the premise that the corneas were susceptible to degeneration by actinic rays. In this regard the youngest brother (Case 3) is of great interest. His right cornea which was clear, may well have been protected from the effect of actinic rays by the ptosed lid. His left cornea, unprotected by a ptosed lid, showed the typical opacification as seen in xeroderma pigmentosa.

It is now known that the skin of patients with xeroderma pigmentosum is most sensitive to light, having a wavelength of 280 to 310 nm (Lynch, 1934). The light of this wavelength has a damaging effect on the DNA molecule. Studies (Cleaver, 1968, 1970; Epstein *et al.*, 1970) indicate that cells of xeroderma pigmentosum are unable to undergo normal repair synthesis of DNA after ultraviolet exposure. The defect may be due to the absence of any enzyme normally present which clears the damaged part of the DNA molecule and allows it to repair. This

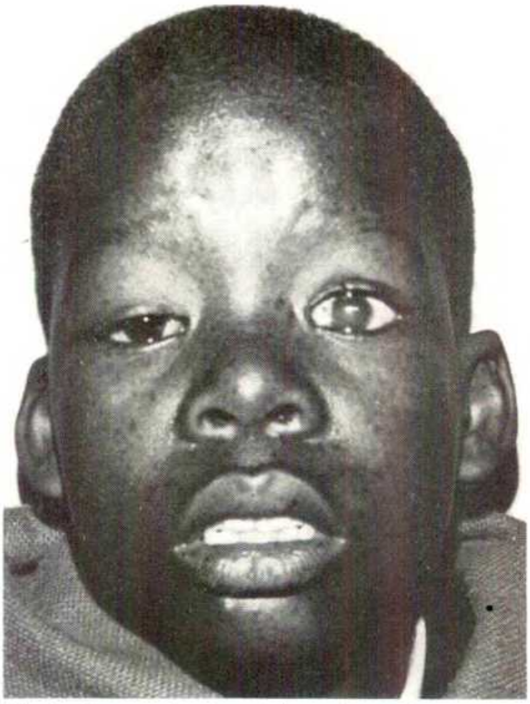

Fig. 5 *Youngest brother with xeroderma pigmentosum*

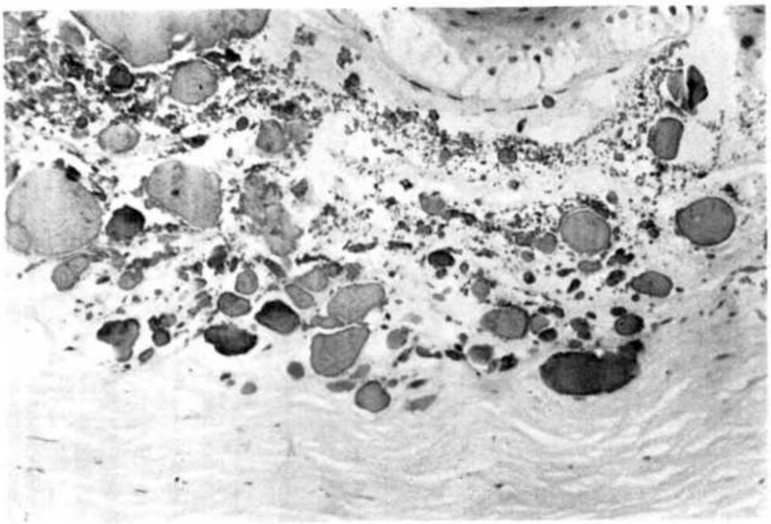

Fig. 6 *Hyaline deposits in superficial stroma with irregularity of superficial stroma*

enzyme defect may be responsible for the corneal damage seen in xeroderma pigmentosum and perhaps for the occurrence of band-shaped nodular dystrophy of the cornea in the case reported. The enzyme defect may be genetically determined in xeroderma pigmentosum and possibly occurs as an ageing process in cases of band-shaped nodular dystrophy not occurring in association with xeroderma pigmentosum, as most of the cases of nodular dystrophy have occurred in elderly patients. However, this is speculation, but the occurrence of 2 actinically determined corneal degenerations in the same patient may indicate a similarity in aetiology not previously suspected.

The treatment of both xeroderma pigmentosum and band-shaped nodular dystrophy is surgical, which is done for optical purposes in the late stages of both conditions.

I thank the Medical Superintendent of the Baragwanath Hospital for permission to publish this paper.

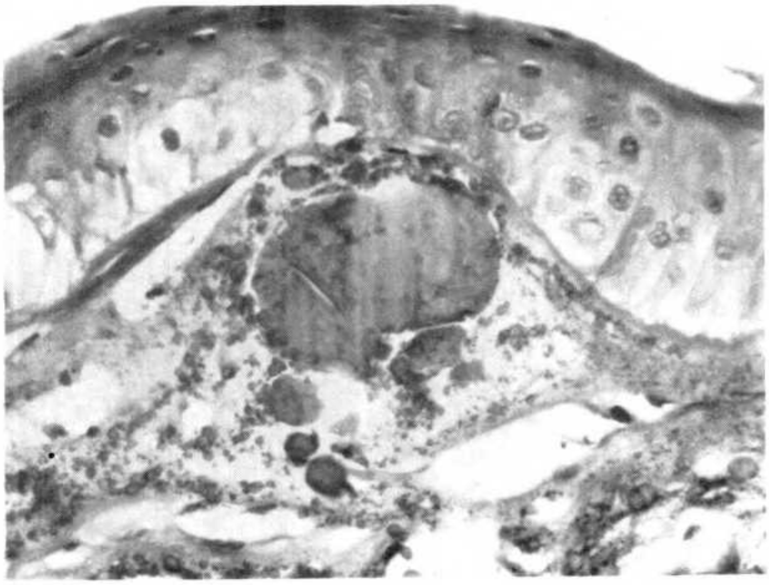

Fig. 7 *Hyaline deposit in stroma eroding basement membrane*

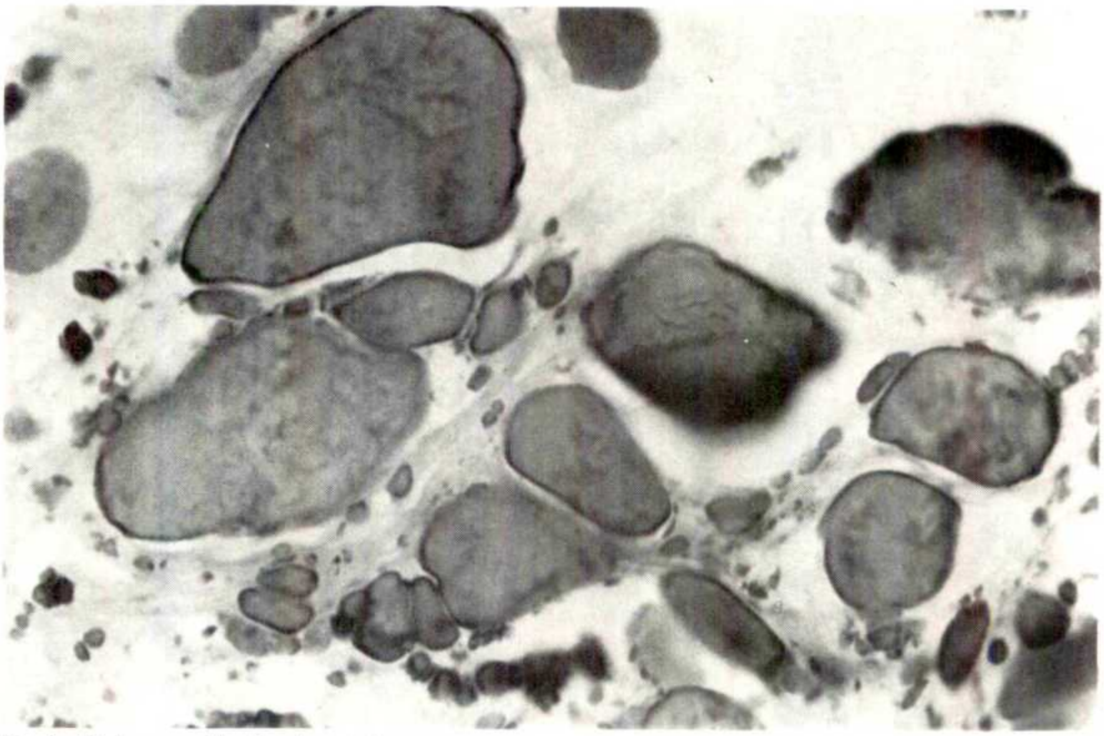

Fig. 8 *High power of hyaline deposits in cornea*

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Peripheral iridectomy in closed angle glaucoma—late complications

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SUMMARY Of 70 eyes with therapeutic peripheral iridectomy (PI), 51% suffered a loss of two or more lines on the Snellen chart; 57% developed posterior synechiae (PS) and 57% showed lens opacities. Thirty-three per cent of eyes that underwent PI prophylactically had a vision drop of two lines or more, 39% developed PS and 42% showed varying degrees of lens opacities. Although vision drop, lens opacities and PS were less marked in the prophylactic group, it appears that PI is a surgical procedure not without its hazards. We therefore suggest that peripheral iridectomy should not be performed routinely on the second eye not suffering an acute attack. This procedure should be undertaken only in cases with positive provocative tests and/or clinical signs of closed angle glaucoma.

For the past 20 years peripheral iridectomy (PI) has been a well-established method in treating closed angle glaucoma. In addition, many perform prophylactic PI routinely on the second eye of a patient who has experienced an attack of closed angle glaucoma, since they consider the procedure to be minor (Chandler and Grant, 1965).

Those who advocate the importance of prophylactic PI refer to a review of 200 cases (Bain, 1957), which shows that in 53% the attack occurred in the second eye within four and a half years. Lowe (1965) estimated that 75% of second eyes are at risk. Both authors confirmed that acute glaucoma attacks occurred in a high percentage of patients in spite of miotic treatment (Bain, 1957; Lowe, 1965).

Peripheral iridectomy, although considered a minor surgical intervention, is not without its complications. Among the late complications are drop of visual acuity, development of posterior synechiae, and possibly accelerated development of lens opacities.

In an attempt to evaluate these late complications of PI we undertook the re-examination of patients in our glaucoma clinic who had undergone this operation.

Material and methods

The investigation was carried out on 225 eyes of 134 patients who had undergone PI with the ab-externo method. Postoperative treatment included mydriatics and topical steroids for four to six weeks. Twenty-three eyes were excluded from the study because macular and corneal changes prevented a proper evaluation. Twenty eyes were not operated upon. The 225 eyes included in the study were sub-divided into two groups: (1) Therapeutic group: 70 eyes operated upon after an attack of closure angle glaucoma. (2) Prophylactic group: 155 eyes, 27 of which were the second eye of patients who had experienced an acute attack of closure angle glaucoma. The remaining 128 eyes had been operated upon after a positive dark-room test.

The follow-up period ranged from one to 11 years (average 4·2 years), with all patients seen in the glaucoma clinic at regular intervals.

The investigation included correction of refractive error, examination of anterior segment, applanation tonometry, and fundus examination. Further examination for synechiae was made after instillation of Neosynephrine (phenylephrine) 10%.

Results

The ages in our study group ranged from 40 to 79 years (mean 65·3 years) with the majority of the patients in the sixth decade. There was a predominance of females (103) over males (31). (Table 1.)

VISUAL ACUITY

Data on visual acuity are presented in Table 2. Both therapeutic and prophylactic groups were sub-

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Table 1 *Distribution of patients according to age and sex*

Age (years)	*Male*	*Female*	*Total*
40–49	3	6	9
50–59	7	33	40
60–69	18	47	65
70–79	3	17	20
Total	31	103	134

divided according to duration of follow-up. The first subgroup was observed from one to three years (100 eyes) and the second subgroup from four to 11 years (125 eyes). At the end of the shorter observation period there was a loss of two lines or more in 38% of the eyes with therapeutic PI and in 23% of the eyes that had undergone the same procedure prophylactically. At the end of the longer follow-up period, however, a loss of two lines or more was seen in 62 and 41% of the patients in the therapeutic and prophylactic groups, respectively.

POSTERIOR SYNECHIAE

Posterior synechiae (PS) were looked for attentively at frequent intervals during the first two months after operation, and in every subsequent examination (once in three to six months).

Table 3 depicts the presence of PS. The cases where information concerning PS was insufficiently recorded were categorised as 'unknown'. The incidence of PS immediately after operation was 42% in the therapeutic group and 17% in the prophylactic group. At the end of the observation period the frequency of PS was 57 and 39%, respectively. In a number of eyes in both groups there was no evidence of PS two months after operation, but it was demonstrated in one of the subsequent routine examinations months or even years later.

Table 4 represents the percentage of eyes with a drop in visual acuity as related to PS at the end of the observation period. A loss of two lines or more on the Snellen chart was recorded in 56% of eyes with PS and in 27% of eyes without this complication.

LENS OPACITIES

Only eyes where the visual drop could be attributed to lens opacities were included in this study. Eyes with mature and progressive cataract preventing

Table 4 *Visual drop and posterior synechiae**

	% of eyes			
Visual drop in number of lines	*With posterior synechiae*	*Without posterior synechia*	*Unknown*	*Total number of eyes*
0	33	46	21	96
1	43	41	16	30
≥2	56	27	17	99

*Visual drop was measured as number of lines lost on the Snellen chart.

Table 2 *Vision drop following peripheral iridectomy**

	Therapeutic group			*Prophylactic group*		
Duration of follow-up	*Visual drop in number of lines*	*No. of eyes*	*% of eyes*	*Visual drop in number of lines*	*No. of eyes*	*% of eyes*
	0	9	30	0	43	62
1 to 3 years (100 eyes)	1	10	32	1	10	15
	≥2	12	38	≥2	16	23
	0	8	20	0	35	40
4 to 11 years (125 eyes)	1	7	18	1	16	19
	≥2	24	62	≥2	35	41

*Vision drop was measured as number of lines lost on Snellen chart.

Table 3 *Development of posterior synechiae following peripheral iridectomy*

		With posterior synechiae		*Without posterior synechiae*		*Unknown*	
		No. of eyes	*% of eyes*	*No. of eyes*	*% of eyes*	*No. of eyes*	*% of eyes*
Therapeutic group (70 eyes)	After operation	29	42	32	46	9	12
	Last examination	40	57	16	23	14	20
Prophylactic group (155 eyes)	After operation	27	17	113	72	15	11
	Last examination	61	39	66	43	28	18

fundus examination were included in the survey when previous data did not indicate significant macular changes.

After observation periods of one to three years lens opacities were found in 45 and 23% of the therapeutic and prophylactic groups, respectively (Table 5), while after four to 11 years the frequency was 67 and 58%, respectively. Progressive cataract was found in 28% and mature cataract in 19% of patients in the therapeutic group, as compared to 12 and 8%, respectively, in the prophylactic group (Table 6).

INTRAOCULAR PRESSURE

Intraocular pressure (IOP) was considered adequately controlled when the tension was less than 24 mmHg. IOP remained within those limits in all eyes (Table 7). Seventy per cent of patients in the therapeutic group received treatment in order to control and maintain the tension. Of the prophylactic group only 35% of the patients needed treatment. No definite cupping or significant visual field loss was noted.

Table 5 *Incidence of lens opacities after peripheral iridectomy*

	Incidence of lens opacities	
Duration of follow-up	*Therapeutic group*	*Prophylactic group*
1–3 years (100 eyes)	14/31 (45%)	16/69 (23%)
4–11 years (125 eyes)	26/39 (67%)	50/86 (58%)

Table 6 *Incidence of progressive* and mature† cataract after peripheral iridectomy*

	Therapeutic group		*Prophylactic group*	
Time	*Progressive cataract (%)*	*Mature cataract (%)*	*Progressive cataract (%)*	*Mature cataract (%)*
Before operation	6·0	7·0	5·2	4·3
End of follow-up period	28·0	19·0	12·0	8·0

*Progressive cataract—vision 6/20 to 6/30.
†Mature cataract—vision 6/60 or less.

Table 7 *Intraocular pressure at the end of the follow-up period*

	Controlled IOP				
	With treatment		*Without treatment*		
	No. of eyes	*% of eyes*	*No. of eyes*	*% of eyes*	*Uncontrolled IOP*
Therapeutic group	49	70	21	30	0
Prophylactic group	54	35	101	65	0

Table 8 *Late complications after peripheral iridectomy at the end of the observation period*

	Therapeutic group		*Prophylactic group*	
	Fraction of eyes and per cent		*Fraction of eyes and per cent*	
Vision loss ≥2 lines	36/70	51%	55/155	35%
Posterior synechiae	40/70	57%	60/155	39%
Lens opacities	40/70	57%	66/155	42%
Mature cataract	13/70	19%	12/155	8%

Discussion

The present study was undertaken in an attempt to evaluate late complications of peripheral iredectomy.

The predominance of women (77%) in our series is in accordance with the higher incidence of closed angle glaucoma in females (67%) (Duke-Elder, 1969b).

Some reports record no vision loss after PI (Goshal and Blaxter, 1969; Primrose, 1960; Douglas and Strachan, 1967), while Lowe (1962) observed a drop in vision of varying degrees in eight out of 58 eyes in which PI was performed therapeutically and in one out of 64 eyes in which surgery was carried out prophylactically. A recent publication by Lowe (1973) reports visual acuity of 6/12 five years after prophylactic PI in 90% of the eyes. Williams *et al.* (1968) reported vision loss of two or more lines in 19% of eyes after a follow-up period of one to six years. However, in our study a vision drop of two lines and more was seen in 33% of the eyes that had undergone prophylactic PI, and in 51% of the therapeutic group (Table 8). In both groups loss of vision became more pronounced with protracted observation time, indicating that the time factor was important in acuity drop (Table 2). Vision loss may be attributed to posterior synechiae and to accelerated lens opacification (see below).

Posterior synechiae are a fairly common finding after PI, ranging from 33 to 49% in the therapeutic patients and from 17 to 19% in the prophylactic group (Goshal and Blaxter, 1969; Phillips and Snow, 1967). Lowe reported PS in six out of 26 eyes that underwent prophylactic PI, while others (Goshal and Blaxter, 1969; Primrose, 1960; Douglas and Strachan, 1967) thought PS to be a negligible complication. However, in our series PS was found in 57% of the therapeutic and in 39% of the prophylactic group (Table 3). In both groups the incidence of PS increased with the passage of time. There was no marked difference in PS formation between eyes receiving steroids subconjunctivally postoperatively and those that did not. It did not appear to us that a broad PI had a greater predisposition for developing PS than a small PI (Phillips and Snow, 1967). A possible cause for PS developing months or years after operation with no obvious ocular inflammation, as seen in our study (Table 3), may have been the prolonged administration of pilocarpine (Duke-Elder, 1962a). Vision loss of two or more lines was more frequently apparent in patients with PS (56%) than in those without (27%) (Table 4). It seems to us that PS plays a role in visual deterioration, as has been suggested by Phillips and Snow (1967), who found that when observation time ranged from four to eight years the average visual drop was one line on the Snellen chart in eyes without PS and two lines in eyes with PS.

Lens opacities were recorded by Lowe (1973) in ten out of 26 eyes (37%) five years following prophylactic PI. In our prophylactic group this disorder was observed in 42% (Table 8), which is in agreement with Lowe's findings. In the therapeutic group lens opacities occurred in a higher percentage of patients.

There is good correlation between PS, lens opacities, mature cataract, and vision drop (Table 8). This may indicate a possible influence of PS on accelerated cataract formation and vision drop.

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Mixed glaucoma

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SUMMARY Two hundred and sixty-seven eyes which underwent peripheral iridectomy for presumed angle-closure glaucoma were investigated. The diagnosis of angle-closure glaucoma was confirmed postoperatively in 258 eyes, in 201 of which the intraocular pressure became normal without further treatment and in 57 of which the postiridectomy IOP was elevated because of visible damage to the anterior chamber angle. Three eyes had open-angle glaucoma with a narrow angle. Six eyes had possible mixed (combined mechanism) glaucoma (2·2%). Mixed glaucoma is a rare, fortuitous combination of open-angle and angle-closure glaucoma rather than a distinct entity, and it might be advisable to avoid the term, which tends to be used for primary glaucomas of uncertain classification.

The primary glaucomas have been classified into 3 groups: open-angle glaucoma, angle-closure (narrow-angle) glaucoma, and combined mechanism or mixed glaucoma (Shaffer, 1960). Since the heredity and pathogenesis of open-angle glaucoma and of angle-closure glaucoma are completely different, their coexistence should be a rare, chance combination. On the other hand most physicians would agree that the diagnosis of mixed glaucoma is made not uncommonly, especially when the differential diagnosis between open-angle and angle-closure glaucoma is uncertain.

A promising method for assessing the incidence of mixed glaucoma is to study eyes which have undergone peripheral iridectomy: if angle-closure glaucoma was definitely present before the iridectomy and if glaucoma was still present post-iridectomy in spite of an open, normal angle, the diagnosis of mixed glaucoma is probable.

We could find no report of such an investigation in the literature.

Materials and methods

The records of 159 consecutive patients who underwent peripheral iridectomy for (presumed) primary angle-closure glaucoma were reviewed. Patients in whom the intraocular pressure (IOP) was higher than 20 mmHg on any occasion following iridectomy and in whom the elevated IOP was not clearly due to the presence of goniosynechiae obliterating a significant part of the angle were recalled for study. The examination of these patients consisted of applanation tonometry without and with treatment, examination of the optic disc and visual fields, and detailed gonioscopy. In most cases gonioscopy was performed by two physicians.

Altogether 267 eyes of 159 patients underwent peripheral iridectomy. There were 89 males and 70 females; 95 eyes had had acute angle-closure glaucoma, 125 eyes had (presumed) intermittent or chronic ('creeping') angle-closure glaucoma, and 47 eyes were fellow eyes of patients who had suffered acute glaucoma in one eye.

The results of peripheral iridectomy are summarised in the table. Of the 267 eyes 258 have pure, angle-closure glaucoma. In 201 of these eyes the IOP became normal after iridectomy, in 42 eyes the IOP remained elevated after iridectomy owing to the presence of extensive goniosynechiae, and in 15 eyes the IOP remained elevated and gonioscopy showed visible damage to the angle in the absence of goniosynechiae. This damage consisted of irregularly distributed, coarse granules and patches

Table *Results of peripheral iridectomy in 267 eyes*

	Eyes	*Eyes*
Normal IOP following iridectomy		201
Elevated IOP following iridectomy with gonioscopic pathology:		
Quarter to half of angle closed by goniosynechiae	14	
More than half of angle closed by goniosynechiae	28	
Visible damage to angle without goniosynechiae	15	57
Elevated IOP with normal angle:		
Misdiagnosed open-angle glaucoma	3	
Possible mixed glaucoma	6	9
Total		267

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of pigment covering all of the angle structures including Schwalbe's line, the anterior and posterior parts of the trabecular meshwork, the scleral spur, and the ciliary body. This distribution of pigment distinguishes a damaged angle from a heavily pigmented but otherwise normal angle in which pigment is precipitated on Schwalbe's line and the functional, posterior part of the trabeculum.

In 9 of the 267 operated eyes the IOP remained elevated after iridectomy in spite of an open, apparently normal angle. In 3 of these eyes the preoperative picture was that of elevated IOP with a narrow (grade 1) but open angle, and the final diagnosis was therefore open-angle glaucoma. In 6 eyes (of 3 patients) the preoperative IOP was between 23 and 32 mmHg, the anterior chamber was narrow grade 1, there was no history of acute angle-closure, and one or more provocative test was strongly positive (elevation of IOP of 10 to 22 mmHg during the test). In 2 eyes the mydriatic test was positive, in 2 eyes the prone-position test (Hyams *et al.*, 1968) was positive, and in 2 eyes both the dark-room and prone-position tests were positive. In all of these 6 eyes the IOP not only remained elevated but was completely uninfluenced by the performance of an iridectomy. These 6 eyes should therefore be regarded as having *possible* mixed glaucoma, since the correct diagnosis could also be open-angle glaucoma with false-positive provocative tests.

Discussion

The prevalence of open-angle glaucoma in subjects over the age of 40 years is 0·5 to 0·6% (Pollack, 1968; Hyams *et al.*, Keroub, 1976). One would therefore expect open-angle glaucoma to be a factor in not more than 0·6% of patients with angle-closure glaucoma.

Abrams (1961) found that 47 out of 1861 consecutive cases of primary glaucoma had been diagnosed as mixed glaucoma but that the diagnosis could be substantiated in only 5 patients—after careful reanalysis with particular attention to a history of haloes and attacks, the dark-room test, and (in 2 cases) the response to iridectomy.

The diagnosis of mixed glaucoma is complicated by the possibility that repeated episodes of angle closure may cause damage to the trabecular meshwork, which is not gonioscopically visible. Such damage would reduce the outflow facility and introduce an element of apparent open-angle glaucoma (Becker and Shaffer, 1965; Chandler and Grant, 1965).

In the present study we found visible signs of damage to the anterior chamber angle in 15 eyes in which no goniosynechiae were present. In the absence of visible evidence of angle damage these 15 eyes would have been diagnosed as having mixed glaucoma.

Out of the 267 eyes investigated 6 may have mixed glaucoma (2·2%). This figure must be regarded as a maximum, since in all 6 eyes the angle-closure element was diagnosed on the basis of provocative tests, which can occasionally produce false positive results. In none of the 6 eyes was there any other direct evidence of angle-closure.

The study confirms the concept that mixed glaucoma is not a separate entity but a chance coexistence of open-angle and angle-closure glaucoma. In the interests of clear thinking it is important to distinguish between the rare cases of mixed glaucoma and the commoner cases of primary glaucoma of uncertain classification. From the practical, therapeutic point of view such a distinction is less important, since the treatment of choice in both cases is peripheral iridectomy followed if necessary by the use of the full range of antiglaucoma drugs and, occasionally, by a filtering procedure.

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The optic disc in glaucoma, II: Correlation of the appearance of the optic disc with the visual field

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SUMMARY Examination of stereoscopic optic disc photographs allowed accurate prediction of glaucomatous and normal fields to be made in 82 and 95% of eyes respectively and for visual field loss to be correctly located in upper and lower half in 83 and 91% of cases respectively. Despite this high correlation the existence of false positive and false negative predictions means that the total reliance on optic nerve examination without visual field estimation in the evaluation of the glaucoma patient should *not* be made. Optic disc examination is too insensitive for long-term follow-up of visual function in a glaucoma patient.

The high correlation between the state of the visual field and the optic disc means that, in the evaluation of the visual functions of a glaucoma patient, the appearance of the optic disc and the visual field should be in agreement.

All therapy for glaucoma is directed against visual loss as that aspect of glaucomatous disease which is functionally incapacitating. Sophisticated methods of assessing the field of vision have allowed recognition of the characteristic scotomata that are the early signs of visual damage. Correct evaluation of visual field defects, however, is time consuming and of necessity subjective. Much recent attention has been directed towards the optic disc because of the more objective nature of the observation. As a result attempts have been made to correlate glaucomatous damage visible on the optic disc with change in the visual field in the hope of increasing the understanding of the disease and improving the care of the patient.

In one recent study, using monocular disc photographs, a series of changes at the optic disc were described which were quite reliably associated with visual field loss (Read and Spaeth, 1974). In other studies, where stereoscopic disc photographs (Douglas *et al.*, 1974) or a combination of stereoscopic funduscopy and monocular disc photographs were used (Hoskins and Gelber, 1975), correct prediction of visual field loss was achieved in 85 and 84% of cases respectively.

This paper reports the accuracy of predicting visual field loss from an analysis of stereoscopic disc photographs of 504 eyes from 252 patients. This material has been used as a basis for a previous report (Hitchings and Spaeth, 1976a), where the optic discs were categorised on the basis of their morphological appearance. This report looks at the accuracy of the disc-field correlation for each optic disc category and shows that prediction of the visual field is considerably more accurate for some of these categories than others. Reasons for incorrect visual field prediction are analysed. It is concluded that disc-field correlation is insufficient to allow reliance on examination of the optic disc alone in the management of glaucoma, but when visual function of a glaucoma patient is being evaluated the appearance of the optic disc and visual field should be in agreement.

Materials and Methods

The stereo photographs from 252 patients (504 eyes) were used. The population comprised 227 patients whose intraocular pressure was consistently greater than 21 mmHg and 25 patients ophthalmologically normal. The stereo pairs were examined without the

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diagnosis being known. The opposite eye of the same patient was available for comparison, providing a test not dissimilar from routine clinical evaluation. Visual field loss was predicted when marked thinning, total absence, or localised pallor of the neuroretinal rim was observed. A fuller analysis of these features has already been discussed (Hitchings and Spaeth, 1976a). The location of visual field defects was based on the known spatial localisation of nerve fibres in the retina and optic papilla (Traquair, 1944; Hoyt and Luis, 1962; Wolff, 1968; Read and Spaeth, 1974; Lynn, 1975). Visual field defects were placed in the upper or lower half of the visual field by observing those signs suggesting field loss on the corresponding lower or upper half of the optic disc.

The predicted field was compared with the actual field obtained on the same day as the photographs. The actual field was plotted on a Goldmann perimeter, 3 isopters being measured in a standardised fashion. The method has been fully described elsewhere (Spaeth, 1975) and is based on that described by Rock *et al.* (1973).

Table 1 *Correlation of visual field with optic disc type:* (a) *Eye with visual field loss*

Optic disc type	*Total no. eyes*	*Actual no. with field loss*	*No. of eyes correctly predicted to have visual field loss*		*False − ve*
Cupping without neuroretinal rim pallor	124	22	12		2
Overpass	44	14	11		1
Cupping with neuroretinal rim pallor	68	60	58		6
Focal notching of the neuroretinal rim	23	23	23		0
Bean-pot	14	13	13		0
Total no. eyes with visual field loss		132	117	82%	

Table 2 *Correlation of visual field with optic disc type:* (b) *Eye with a normal visual field*

Optic disc type	*Total no. eyes*	*No. with normal field*	*No. of eyes correctly predicted to have a normal field*		*False − ve*
Normal	231	231	231		0
Cupping without neuroretinal rim pallor	124	102	102		8
Overpass	44	30	29		3
Cupping with neuroretinal rim pallor	68	8	2		4
Bean-pot	14	1	1		0
Total no. eyes with normal field		372	365	95%	

Results

82% of eyes with visual field loss and 95% of eyes with normal fields were correctly identified. Correct location of a visual field defect to the upper or lower half of the field was achieved in 83·5 and 91% of eyes respectively. The results of comparing eyes with and without visual field loss with optic disc 'types' may be seen in Tables 1 and 2 respectively. It will be seen that 'focal notching' in the neuroretinal rim was always associated with visual field loss. Fig. 1 is a

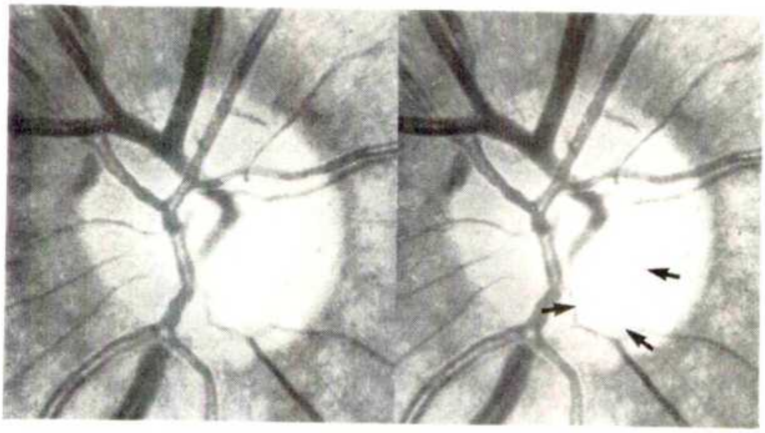

Fig. 1 *Stereophotograph illustrating 'focal notching', an inferotemporal notch, or extension of the cup, is present (arrowed). Adequate visualisation of these stereo-pairs may be obtained by holding a suitable convex sphere in front of each eye, decentred sufficiently to give fusion*

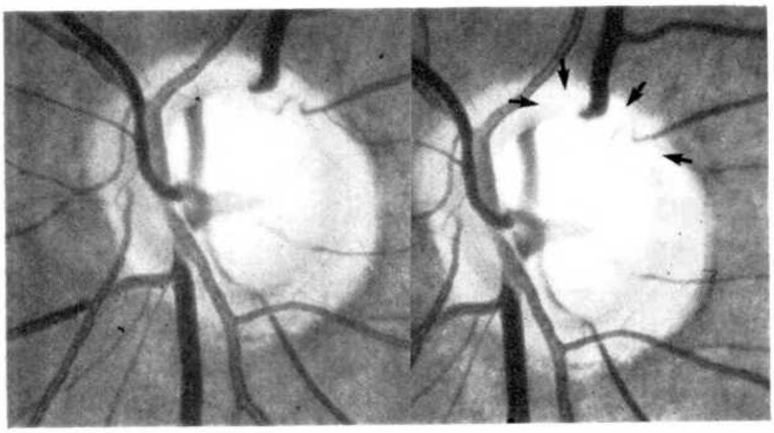

Fig. 2 *Stereophotograph illustrating 'cupping with pallor' (arrowed) in a patient with an inferior arcuate scotoma*

stereophotograph of an optic disc with focal notching that had a corresponding upper arcuate scotoma. The detection of 'pallor' on the neuroretinal rim in conjunction with glaucomatous cupping was also a good indicator of visual field loss. 58 of the 60 eyes classes as 'cupping with pallor' were correctly predicted to have visual field loss. Fig. 2 is a stereophotograph of an eye demonstrating cupping with pallor that had visual field loss. The prediction of visual field defects was less accurate in those eyes with 'cupping without pallor'; whereas glaucomatous cupping with localised absence of the neuroretinal rim would always be associated with a corresponding field defect, thinning of the neuroretinal rim without obvious pallor was often seen without field loss. (Fig 3 is a stereophotograph of an eye with localised absence of the neuroretinal rim at the upper pole and thinning of the neuroretinal rim without pallor at the lower pole.) Out of 22 eyes demonstrating cupping without pallor only 12 were correctly stated to have field loss.

Table 3 correlates the predicted location of field defects in the upper and lower halves of the visual field with optic disc type. It may be seen that most errors occurred with the optic discs designated 'cupping with' and 'cupping without pallor' of the neuroretinal rim.

Discussion

It is proposed to look at features in the optic disc suggesting visual field loss and discuss possible sources of error.

FEATURES SUGGESTING VISUAL FIELD LOSS

Glaucomatous enlargement of the optic cup frequently follows a pattern of vertical extension of the orifice of the cup (Chandler and Grant, 1965; Kronfield, 1967; Kirsch and Anderson, 1973; Wiseman *et al.*, 1973). Deepening of the cup (Portnoy, 1975) with an increase in the steepness of the walls may also be present. All these factors con-

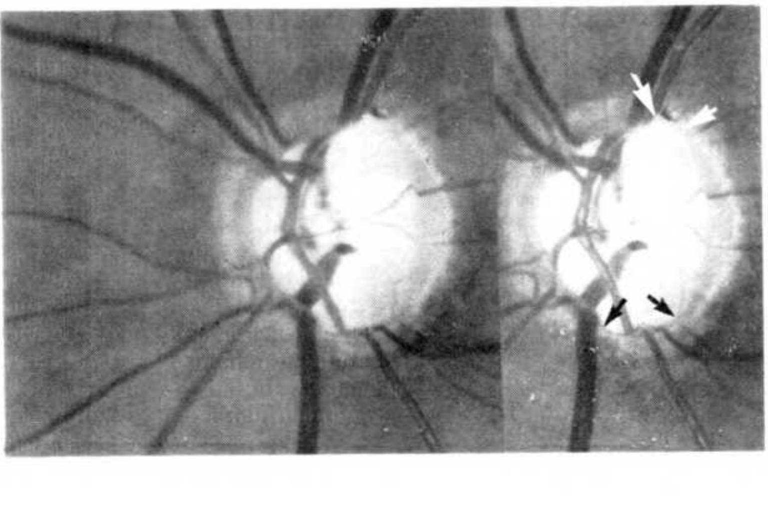

Fig. 3 *Stereophotograph illustrating localised absence of the neuroretinal rim at the upper pole (white arrows) and localised thinning of the neuroretinal rim at the lower pole (dark arrows) in an eye with upper and lower scotomata*

Table 3 *Correlation of location of visual field loss with optic disc type*

Optic disc type	*Upper half field loss*			*Lower half field loss*		
	Actual field loss (103 eyes)	*No. of eyes correctly predicted to have field loss (89 eyes, 83·3%)*	*False −ve*	*Actual field loss (68 eyes)*	*No. of eyes correctly predicted to have field loss (62 eyes, 91%)*	*False −ve*
Cupping without pallor of the neuroretinal rim	16	12	0	14	8	0
Overpass cupping	7	7	1	9	8	0
Cupping with pallor of the neuroretinal rim	48	38	13	40	40	6
Focal notching	23	23	0	0	0	0
Bean-pot cupping	9	9	0	5	6	1

tribute to an increase in the total volume of the cup (Portnoy, 1975) without there necessarily being extensive loss of neuroretinal rim. Such changes are recognisable before detectable field loss (Kronfeld, 1967; Fishmann, 1970; Kolker and Hetherington, 1970; Portnoy, 1975). The prediction of field loss in a glaucomatous eye was based on identifying sites from which neuroretinal rim tissue had been lost. This was seen as thinning, absence, or pallor of the neuroretinal rim tissue.

The results obtained in this study show a very high correlation between observation of these signs on the neuroretinal rim of the optic disc and visual field loss. The figures of 82% of discs with and 95% without field loss are in general agreement with studies carried out by Douglas *et al.* (1974) and Hoskins and Gelber (1975), who correctly forecast 85 and 84% of discs with field loss and 80 and 97% without field loss respectively. These figures are *not* good enough to place total reliance on optic disc examination to the exclusion of visual field testing when evaluating a glaucoma patient.

The correct location of field defects in upper and lower halves of the visual field was achieved in 83·5 and 91% of eyes respectively. More precise location of defects within the visual field based on optic disc examination would be subject to far greater error, because of the difficulty in equating small field defects with a specific area on the neuroretinal rim. Reliance on optic disc morphology alone for long-term management would be quite insufficient, as minor changes in the visual field would not be likely to cause visible change on the neuroretinal rim of the optic disc; the false positive and negative readings could induce overtreatment and the withholding of treatment respectively in some cases.

SOURCES OF ERROR

The accuracy of spotting visual defects by evaluation of the optic disc is sufficiently high to warrant a closer look at the sources of error. Evaluation of possible errors point to three major sources. Firstly, errors inherent in the methods used to examine the visual field and optic disc. Secondly, non-glaucomatous causes for visual field loss. Thirdly, the variable response of the optic nerve in glaucoma.

Errors in clinical examination

Errors inherent in visual field examination are notorious. This is particularly important with the early isolated scotomata that occur in glaucoma, and may have contributed to some of the incorrect predictions in this series. Visual field testing is an art, 'requiring a degree of psychic evaluation that will determine the validity of its findings' (Harrington, 1975).

Magnified stereophotographs of the optic disc provide a good and accurate method of recording detail. However, some detail is lost. The photographs are not true stereoscopic photographs, as they are taken consecutively, and an erroneous impression of the shape of the optic cup may occur because of eye movements and/or variations in the separation of the camera angle.

Examination of the stereo pairs is open to human error with subtle glaucomatous changes being overlooked. In several instances, repeat examination of the optic disc, on this occasion with knowledge of the visual field, allowed recognition of those signs described above that suggest visual field loss.

The wide field of illumination that occurs with fundus photography allows light from the peripapillary choroid to 'colour' adjacent disc tissue (Gloster and Parry, 1974). In a few eyes where the neuroretinal rim appeared pink on the fundus photograph slit-lamp examination of the optic disc using a narrow light beam revealed localised pallor. These instances accounted for some of the failures to predict the existence of a field defect in this study.

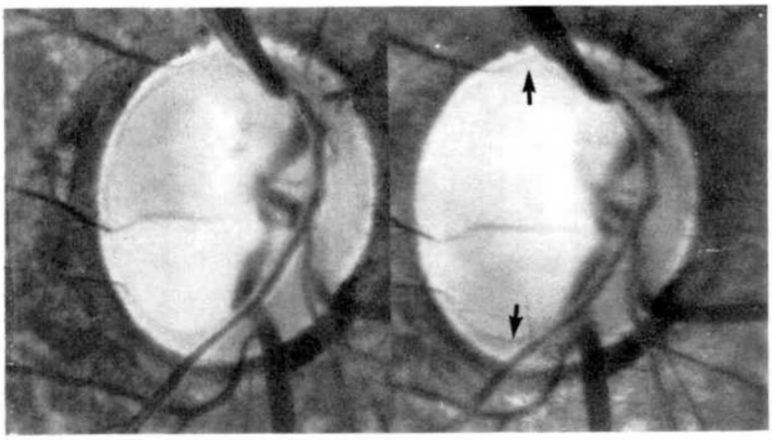

Fig. 4a *Stereophotograph illustrating 'bean-pot' cupping. Notice relative thickness of neuroretinal rim at upper and lower poles (arrowed).*

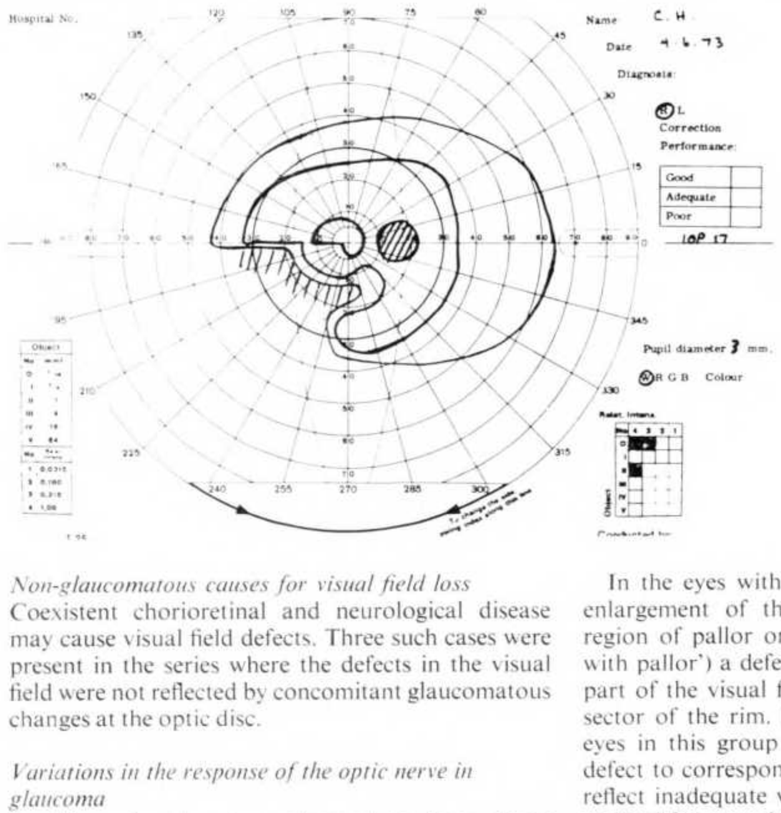

Fig. 4b *Corresponding visual field*

Non-glaucomatous causes for visual field loss
Coexistent chorioretinal and neurological disease may cause visual field defects. Three such cases were present in the series where the defects in the visual field were not reflected by concomitant glaucomatous changes at the optic disc.

Variations in the response of the optic nerve in glaucoma
In this series the eyes observed to have 'focal notching' (Hitchings and Spaeth, 1976a) in the neuroretinal rim were always found to have an associated defect in the visual field. In these eyes the neuroretinal rim appeared normal except in the affected sector, where it was considerably thinned. The discovery of a localised notch despite a 'normal' field merits searching the visual field until the glaucomatous defect is found.

In the eyes with evidence of a more generalised enlargement of the optic cup associated with a region of pallor on the neuroretinal rim ('cupping with pallor') a defect could usually be found in that part of the visual field corresponding with the pale sector of the rim. However, a small proportion of eyes in this group did *not* have a recordable field defect to correspond with the pale sector. This may reflect inadequate visual field testing, itself a coarse method for assessing visual function or an incorrect assumption that pallor always means atrophy. Neuroretinal rim pallor is commonly associated with hypofluorescence, but small areas of hypofluorescence of the neuroretinal rim do not always have an associated visual field defect. (Hitchings and Spaeth, 1976b).

The greatest difficulty in predicting the state of the visual field from examination of the optic disc came from the group entitled 'cupping without pallor.' This group is important because it contains optic discs similar in appearance to the optic discs whose optic cups decreased in volume following control of intraocular pressure (Kolker and Hetherington, 1970; Armaly, 1975), suggesting 'regression' of the optic nerve disease.

As has already been discussed, a proportion of optic discs demonstrating cupping without pallor may be seen on slit-lamp examination to have sector pallor of the neuroretinal rim to correspond with the visual field defect. This is one reason why slit-lamp examination is an essential part of the glaucoma examination. Even with slit-lamp examination difficulty arises in recognising morphological changes in the pink neuroretinal rim that are of sufficient severity to be associated with loss of visual field.

In an individual case a large optic cup is not necessarily a sign of visual field loss. A large optic cup may be developmental and reflect a greater than usual diameter of the optic disc. Because the neurones comprising the neuroretinal rim are relatively constant in number, they have a constant cross-sectional area. The greater the optic disc diameter the larger the cup and proportionately smaller the neuroretinal rim.

In normal individuals a large optic cup in one eye is mirrored by a similarly sized cup in the fellow eye (Hitchings and Spaeth, 1976a). Acquired enlargement of the optic cup (Hitchings and Spaeth, 1976a) may be detected before visual field loss and may simultaneously affect the orifice, walls, and floor. The optic cup can form a large proportion of the volume of the intraocular part of the optic nerve before field loss is demonstrated. The most extreme example is seen in eyes with 'bean pot' cupping, where, although the cup may be very large, the amount of visual field loss appears disproportionately small (Fig. 4). In these cases such localised thinning or absence of the neuroretinal rim provides a clue to possible field loss. In the one eye within the series reported with a normal field despite 'bean pot' cupping the neuroretinal rim appeared of similar thickness and uniform colour throughout. The 'undermining' of the neuroretinal rim that exists in these optic nerves is not an indicator of visual field loss. At what stage it is associated with field loss cannot be ascertained as it is hidden behind the neuroretinal rim.

In eyes with 'cupping without pallor' the optic disc will show acquired enlargement of the cup. Clues to the state of the visual field are found in variations in neuroretinal rim thickness rather than the slope of the walls or the depth of the optic cup. Careful examination of the contours of the neuroretinal rim will suggest the presence or absence of visual field loss. If there is no visual field defect the neuroretinal rim will appear to be of equal thickness throughout or show gradual variations rather than abrupt changes in thickness when passing from one part of the rim to another (Fig. 5). When a visual field defect is present, the neuroretinal rim will often demonstrate abrupt changes in thickness when passing from one part of the rim to the next. In this instance it is the thin neuroretinal rim, sharply demarcated from adjacent, thicker rim, that has a corresponding visual field defect. (Fig. 6). Despite recognition of these sources of error there remain a few optic discs in eyes with visual field defects that do not show clear-cut changes suggesting visual field loss.

Ancillary evidence comes from examination of the nerve fibre layer. When the layer is visibly intact, the field is normal. When it is possible to detect localised defect in the reflexes arising from the nerve fibre layer, a corresponding defect in the visual field can frequently be detected. Many eyes with glaucoma, however, will have complete depression of reflexes arising from the nerve fibre layer despite full field or localised defects (Hitchings and Spaeth, 1976a).

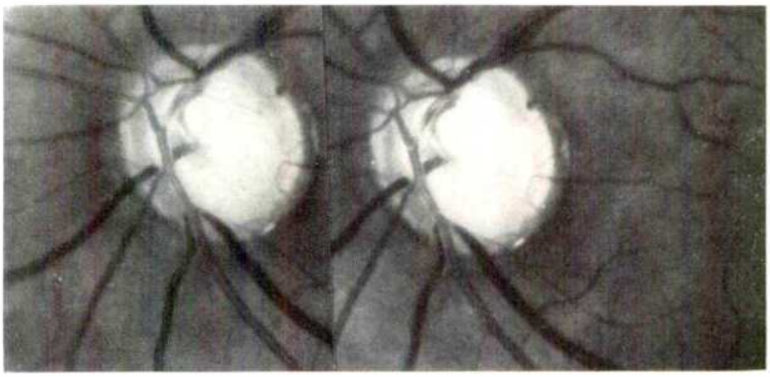

Fig. 5 *Stereophotograph illustrating cupping without pallor. In this case the visual field was normal, the neuroretinal rim shows gradual variations in thickness only*

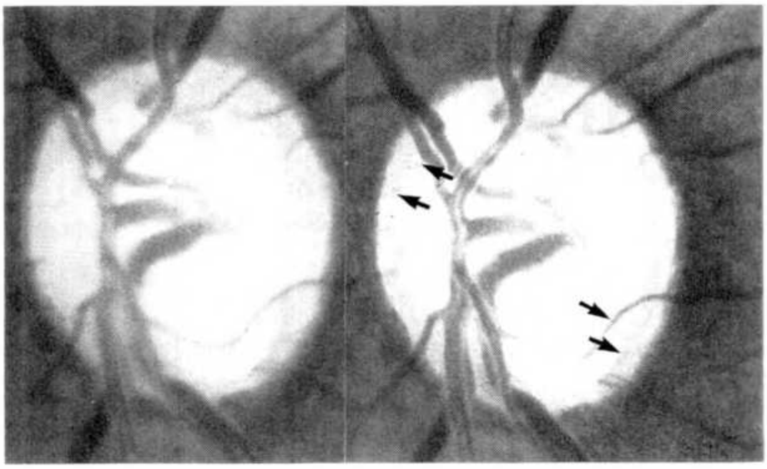

Fig. 6 *Stereophotograph illustrating cupping without pallor, in this case the neuroretinal rim shows sudden thinning at the lower pole (arrowed) corresponding with the upper half visual field defect*

Conclusion

Careful examination of magnified stereo-pair photographs of the glaucomatous disc allows accurate prediction of the presence and absence of visual field loss. The error rate was too high to permit exclusion of visual field examination in the evaluation of a patient with glaucoma, and insufficiently sensitive for long-term follow-up. However, the existence of a good disc-field correlation means that the evaluation of the glaucoma patient is incomplete without ensuring agreement between the appearance of the optic disc and state of the visual field.

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Microhaemangiomas of the iris with spontaneous hyphaema and acute glaucoma

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SUMMARY A case of bilateral microhaemangiomas of the pupillary borders in a 69-year-old woman is described. When first seen she presented with acute angle closure glaucoma and spontaneous hyphaema. Photographs and iris fluorescein angiography are presented and microhaemangiomas are discussed.

Case report

A 69-year-old White woman was referred to the Nassau County Medical Center in July 1975 with a diagnosis of acute glaucoma and spontaneous hyphaema. On the evening before admission she noted decreased vision in the left eye. On awakening the following morning vision had worsened and the eye had become painful. Two hours later her referring ophthalmologist noted a corrected visual acuity of 20/400 in the left eye, a hazy cornea, and a mid-dilated pupil. Immediate treatment included intravenous acetazolamide 500 mg and 2% pilocarpine drops every five minutes for 20 minutes. The ocular history was normal and there was no history of trauma. On examination the physical findings were normal except for mild emphysema.

On admission the corrected visual acuity of the right eye was 20/20–1 and the left eye was 20/200. The intraocular pressure by applanation was 22 mmHg in the right eye compared with 50 mmHg in the left eye. The right eye was normal except for microhaemangiomas at the pupillary border at the 9 o'clock position. The left cornea had microcystic epithelial oedema, and the left pupil measured 3 mm and was poorly reactive to light. The anterior chamber was shallow with a small hyphaema inferiorly and a bleeding site from a prominent cluster of fine vessels at the 2 o'clock position on the pupillary border. These clusters of small vessels were coiled and appeared very thin-walled. These vascular tufts were more prominent in the left eye. Both irides were pale blue with a well defined collarette, and neither showed evidence of rubeosis or persistent pupillary membrane. The lens and posterior segment were unremarkable. Gonioscopy, performed later, showed a closed angle superiorly and an open but narrow angle inferiorly. After 20 minutes the bleeding stopped.

That evening therapy with pilocarpine 2%, oral acetazolamide 250 mg four times a day, and oral glycerol resulted in clearing the corneal oedema and lowering the ocular tension to 20·6 mmHg. The next day the visual acuity of the left eye was 20/25, the cornea and anterior chamber were clear, and the intraocular pressure with applanation was 16 mmHg. The patient was treated with bed rest for an additional four days, during which time the anterior chamber remained clear and the intraocular pressure remained within normal limits despite discontinuation of all antiglaucoma medications.

During the follow-up period there was no recurrence of the hyphaema. A dark-room provocative test showed an increase of 8 mmHg in both eyes and was followed by uneventful bilateral peripheral iridectomies. Postoperative photographs were taken, and fluorescein angiography of the irides was performed (Figs. 1 and 2). Examination of family members contributed no relevant information.

Discussion

Microhaemangiomas, or vascular tufts, are small lesions consisting of minute, tightly-coiled blood vessels with thin, delicate, capillary-like walls that form at the ruff of the pupillary border (Fechner,

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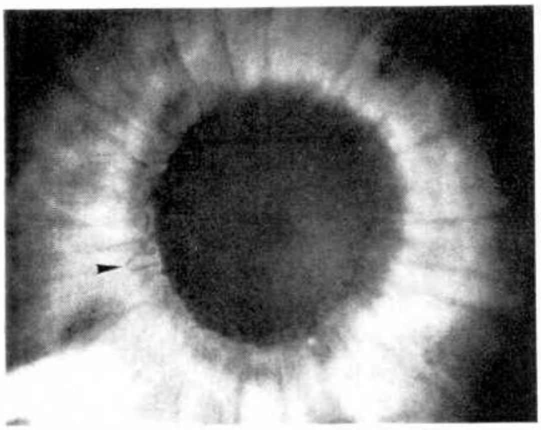

Fig. 1 *Slit-lamp photograph of right eye; microhaemangioma at 9 o'clock meridian (arrow)*

1958; Cobb, 1968; Rosen and Lyons, 1969; Cobb *et al*., 1970; Sellman, 1972; Magauran, 1973; Israel and Lorenzetti, 1974; Savir and Manor, 1975). They may be isolated or may arrange themselves in small clusters that have no tendency toward network formation. Occasionally, the normal pigmentation of the pupillary ruff is altered near the microhaemangiomas (Cobb, 1968). These vascular tufts are uncommon, with approximately 100 cases previously reported (Fechner, 1958; Cobb, 1968; Rosen and Lyons, 1969; Cobb *et al*., 1970; Sellman, 1972; Magauran, 1973; Israel and Lorenzetti, 1974; Savir and Manor, 1975). In our clinical experience and in Sellman's (1972) microhaemangiomas occur in approximately one in every 2000 patients. The majority are bilateral, with only 13 unilateral cases reported (Fechner, 1958; Magauran, 1973; Savir and Manor, 1975). A slight male predominance has been noted, and the onset is usually in the sixth and seventh decades, except in myotonic dystrophy; even when microhaemangiomas accompany this disease, the cases tend to occur in the fourth and fifth decades (Cobb, *et al*., 1970). Among other associated conditions are respiratory disease and possibly diabetes mellitus.

The diagnosis of microangiomas is made from the characteristic morphological appearance of these lesions as seen through the slit-lamp biomicroscope. They are easily missed and are difficult to photograph because of their small size. Fluorescein angiography, however, enables demonstration of a larger number of these lesions than are apparent on slit-lamp examination (Cobb, 1968; Rosen and Lyons, 1969). Although the aetiology remains unknown, it would appear that these lesions are developmental in view of their distinctly higher incidence among the elderly (Cobb, 1968; Cobb, *et al*., 1970).

In no previous report did a patient present with a spontaneous hyphaema and acute glaucoma (Table 1). Magauran (1973) reported a case in which secondary glaucoma developed in association with a recurrent hyphaema several years after the first episode. The size of the hyphaema was not stated. However, despite resolution of the hyphaema and normal findings on ocular examination, including gonioscopy, administration of pilocarpine 4%

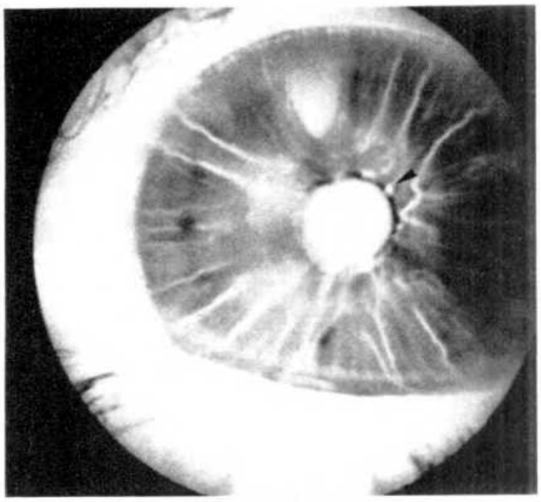

Fig. 2 *Fluorescein angiography of the left eye depicting microhaemangiomas as dots of hyperfluorescence at the pupillary border. Arrow indicates site that previously bled*

Table 1 *Summary of cases of microhaemangioma with spontaneous hyphaema*

Reference		*Age and sex*	*Bilateral*	*Associated findings*	*Fluorescein angiography*
Fechner	(1958)	42 F	No	None	No
Magauran	(1973)	62 M	Yes	Not stated	Yes
Magauran	(1973)	61 F	No	Not stated	Yes
Magauran	(1973)	69 F	Yes	Not stated	Yes
Rosen *et al*.	(1969)	73 M	Yes	Chronic bronchitis, hypertension	Yes
Israel *et al*.	(1974)	60 F	Yes	Mild osteoarthritis	Yes
Sellman	(1972)	45 F	Yes	None	No
Sellman	(1972)	76 F	Yes	Congestive heart failure	No
Savir *et al*.	(1975)	47 F	No	Cavernous haemangioma	Yes

four times a day was necessary to maintain the ocular tension within normal limits. Savir and Manor (1975) reported a case in which the ocular tension increased from 14 to 22 mmHg during an episode of hyphaema secondary to bleeding from a microhaemangioma. Gonioscopic examination disclosed a wide open angle, and the water provocative test was negative. In our case the patient was predisposed to acute glaucoma, and the attack was precipitated by the occurrence of a spontaneous hyphaema. After treatment the tension returned to normal without any medications. It appears likely that the glaucoma or increased intraocular pressure that may occur in a patient with microhaemangiomas and spontaneous hyphaema is either a direct result of the hyphaema or the presence of undiagnosed glaucoma. The presence of microhaemangiomas alone does not seem to be related to an increased incidence of glaucoma.

Owing to the scarcity of reports of iris microhaemangiomas association with spontaneous hyphaema and glaucoma cannot as yet be determined, and only a generalised clinical picture can be given. Perhaps if more attention is directed towards studying these vascular abnormalities questions on their true incidence, aetiology, associated conditions, and prognosis can be fully answered.

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Comparative study of Watson's and Cairns's trabeculectomies in a Black population with open angle glaucoma

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SUMMARY A comparative study of the effectiveness of Watson's and Cairns's trabeculectomy in a Black South African population with open-angle glaucoma is presented. The eventual success rate of 91·6% is comparable with that found in Whites, and the results were similar with both methods.

Conflicting results have been obtained by different authors with filtering operations in Black populations (Iliff, 1944; Berson *et al.*, 1966; Welsh, 1969; and Luntz, 1965). Similarly when reviewing trabeculectomies in Negro eyes the results have been conflicting. Chatterjee and Ansari (1972) had good results on their patients in Ghana using Cairns's trabeculectomy, while Welsh (1972) employing the same technique in South Africa reported only 19% success rate. Freedman (1976) in his series of Watson's trabeculectomy on American Negroes reported an 80% success rate.

We report on the results of a retrospective study comparing the efficacy of the Cairns and Watson types of trabeculectomy, performed on a Black South African population suffering from open angle glaucoma. Although results in this population with the classical filtration operations are good (Luntz, 1965), trabeculectomy has the advantage of fewer postoperative complications.

Materials and methods

A total of 34 patients—22 males and 12 females—their ages ranging from 35 to 75, had surgical treatment. There were 49 eyes on which 61 trabeculectomies were performed. All the patients were seen at the Glaucoma Clinic, St. John Eye Hospital, Baragwanath, and underwent trabeculectomy between 1 January 1974 and 31 December 1975.

In all these patients medical treatment failed to control their glaucoma. Failure was judged by continuing field loss and constantly elevated pressures despite maximal medical therapy. Prior to surgery, all patients were admitted to hospital and diurnal curve studies on full medication for 4 to 10 days were done.

The surgical techniques used were those described by Cairns (1970) and modified by Watson (1972).

The procedure followed was: a conjunctival flap was raised in the upper nasal or upper temporal quadrant and 3 × 3 mm superficial scleral flap of ½ thickness dissected and hinged on the cornea. A flap 2 × 2 mm in size was dissected in the underlying sclera from clear cornea to scleral spur. This deep corneo-scleral flap was excised and a peripheral iridectomy performed. The superficial flap was closed with 4 to 6 10/0 nylon sutures and the conjunctival flap sutured with 10/0 nylon.

When using the Watson procedure (Watson, 1972) dissection of the deep scleral flap (2 × 3 mm) was commenced 1 mm behind the scleral spur dissecting towards the cornea. At the scleral spur the ciliary body was dissected off by blunt dissection producing a cyclodialysis. The flap was dissected forward to clear cornea and then excised.

Both procedures were done using the operating microscope, with zoom-lens facilities. Anaesthesia was either local or general and identical postoperative treatment was given to all patients: cycloplegic and steroid drops 3 to 4 times a day for 10 days.

Results

The follow-up period ranged from a minimum of 6 months to a maximum of 30 months, 24 patients (70·5%) being followed up for more than a year.

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The operation was considered to be successful if intraocular pressure was 20 mm Hg or less, with or without additional medication for the total follow-up period.

Table 1 summarises the results of the two procedures done as the first operation. Both techniques were equally successful in controlling intraocular pressure (Watson's 73·3% and Cairns's 73·6%).

Thirteen of the initial trabeculectomy procedures were failures (Table 1). Of these 12 had a second trabeculectomy, by either the Cairns or Watson method. One patient refused further surgery. The results of these repeated trabeculectomies can be seen in Table 2. Three out of the five reoperations by the Watson technique and five out of the seven by the Cairns method were successful. Therefore of 48 eyes with open angle glaucoma which had one or more operations 44 were eventually controlled by surgery, a success rate of 91·6%.

The average preoperative intraocular pressure was 28·9 mmHg in those patients who had successful Watson type trabeculectomy as compared with 30·9 mmHg in patients who had a successful Cairns procedure. The average preoperative pressure in the failures was 27·8 and 29·3 mmHg respectively.

Thirteen patients (15 eyes) required additional medication to control intraocular pressure after a Watson trabeculectomy and 12 patients (16 eyes) after the Cairns method.

COMPLICATIONS

Complications were minimal in those eyes operated on by the Cairns technique. Only two showed shallow anterior chamber postoperatively, one with a choroidal detachment. These resolved spontaneously within a few days. Those operated on by the Watson method developed more postoperative complications. The commonest was hyphaema. Other complications included shallow anterior chamber (3), all of which resolved spontaneously, severe uveitis, in one eye, and cataract one month after surgery in one eye.

Table 1 *Results of first operations*

	Watson	*Cairns*	*Total*
Number of Operations	30	19	49
Success	22	14	36
Failure	8	5	13
% Success rate	73·3	73·6	73·4

Table 2 *Results of 12 trabeculectomy reoperations*

Watson		*Cairns*		*Total*
Success	*Failure*	*Success*	*Failure*	
3	2	5	2	12

Discussion

The Watson and Cairns methods of trabeculectomy were compared in 49 eyes of Black South African patients with open angle glaucoma. The degree of success after the first operation was similar in both. Watson's method 73·3% and Cairns's method 73·6%.

Trabeculectomy eventually controlled the disease in 91·6% of the eyes subjected to surgery. This result in South African Blacks is far more optimistic than those reported by Welsh (1972) in a similar population and compares favourably with the results of classical filtration operations in the same population (Luntz, 1965), and the more recent report in an American Black glaucoma population by Freedman *et al.* (1976).

These results are similar to the findings of other investigators reporting on White glaucoma populations (D'Ermo and Bonomi, 1973; Thyer and Wilson, 1972; Jerndal and Kriisa, 1974; Ridgway, 1974; and Watson and Barnett, 1975).

Twelve eyes in our series were operated on more than once and of these operations eight were successful. Although these figures are too small to draw meaningful conclusions it seems that repeat trabeculectomies in Black people are more successful than repeat operations in other types of filtration surgery (Luntz, 1970).

The preoperative intraocular pressure does not seem to influence the final outcome, and the drop in pressure after successful surgery was similar with both techniques.

Our analysis has shown that the final postoperative result is similar whether the Cairns or Watson technique is used. The operation of trabeculectomy works well in Black patients with open angle glaucoma. Immediate postoperative complications are fewer with the Cairns technique than with the Watson method. These complications were similar to those described by Ridgway *et al.* (1972) and Watson and Barnett (1975).

Conclusions

From the above study it seems that trabeculectomy is a good procedure in open angle glaucoma in Black South Africans. Irrespective of the type of surgery the final results were the same. There were fewer complications with the Cairns procedure.

We wish to thank the Medical Superintendent of the Baragwanath Hospital for permission to publish.

Thanks are also due to the registrars working in the Glaucoma Clinic for their assistance.

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Implants for draining neovascular glaucoma

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SUMMARY The implant design, surgical technique, and pharmacological methods of controlling bleb fibrosis, used to treat neovascular glaucoma, are described, together with the results of 14 operations performed on 12 eyes.

Established glaucoma with iris neovascularisation and a medically uncontrollable intraocular pressure carries such a poor prognosis that treatment is usually limited to the retrobulbar injection of alcohol or enucleation—even in the presence of slight residual vision. One of us (A.C.B.M.) developed a series of draining implants for use in severe and complex cases of glaucoma (Molteno, 1969a, b; 1970; 1973a, b; Molteno *et al.*, 1976a, b). This communication reports the design of implant and the surgical technique currently used to treat cases of neovascular glaucoma at the Tygerberg Hospital glaucoma clinic and at the University of Edinburgh.

Principles of implant

Among the first attempts to drain cases of glaucoma by an artificial device was that of Zorab (1912), who connected the anterior chamber to the subconjunctival space by means of a silk thread which acted as a 'conducting wick'. This operation of aqueoplasty gave long-term control of intraocular pressure in some cases (Martin and Zorab, 1974). This work has been followed by numerous attempts to drain glaucomatous eyes by a wide range of devices, which can be classified as follows:

(1) Translimbal tubes of various materials connecting anterior chamber to subconjunctival space.
(2) Sheets of gel film and other materials placed beneath the conjunctiva over a conventional drainage operation fistula (e.g., cornea-scleral trephine hole or iridencleisis opening) in order to promote the formation of a large bleb.
(3) Implants of various materials inserted to maintain the patency of cyclodialysis clefts.
(4) Devices draining vitreous from eyes with absolute glaucoma.

Glaucoma implants are reviewed by Ellis (1960), and other recent publications in this field include those of Epstein (1959), La Rocca (1962), MacDonald and Pierce (1965), and Blumenthal *et al.* (1970).

Specifications and mode of action of implants

Our current implant utilises an artificial translimbal tube combined with bleb spreading plate. The translimbal tube of silicone rubber is 16 mm long and has an internal diameter of 0·30 mm and an external diameter of 0·63 mm. It is firmly attached to and opens on to the upper surface of a thin circular acrylic episcleral plate (Stellon brand polymethyl methacrylate) 13 mm in diameter, which has a thickened rim 0·7 mm in height around the circumference. This rim is perforated for attachment of the translimbal tube and to allow passage of sutures which fasten it in position on the globe (Fig. 1).

When used to drain a case of glaucoma, the episcleral plate is sutured to sclera and buried beneath a thick flap of Tenon's capsule and conjunctiva. The translimbal tube is trimmed to the correct length and inserted into the anterior chamber after being buried under a lamellar scleral flap. During the first few days after operation the episcleral plate becomes surrounded by a thin layer of vascular connective tissue which impedes the flow of aqueous away from the plate and causes the intraocular pressure to rise. The increasing pressure causes this fibrovascular 'bleb lining' to become distended and to be stretched by a force that is directly proportional to the product of intraocular (= to intrableb) pressure and radius of curvature of the 'bleb lining' (Young, 1805; Laplace, 1807).

Consequently, if this 'bleb lining' can be prevented

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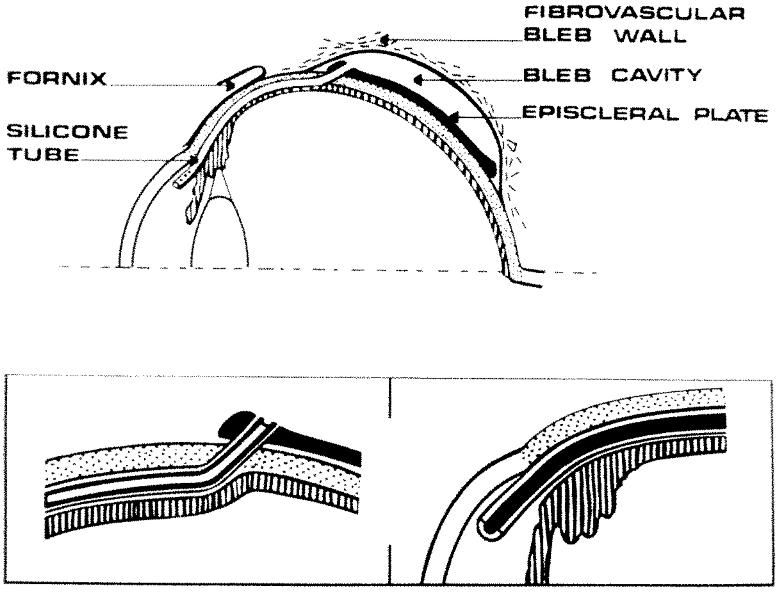

Fig. 1 *Situation and principle of draining implant*

from becoming too thick (by administration of a combination of anti-inflammatory agents), and if the radius of curvature of the bleb lining can be made large through the presence of a large episcleral plate, then a normal intraocular pressure causes progressive stretching and enlargement of this bleb lining until the increased area available for drainage of aqueous so lowers the intraocular (and intrableb) pressure that the bleb lining no longer stretches. This situation results in long-term control of intraocular pressure at a level which depends directly on the area of bleb available for drainage and inversely on the thickness of the fibrous inner bleb lining.

Case selection

We hesitated to operate on eyes with neovascular glaucoma, since a drainage operation with insertion of foreign material (albeit inert plastic) into an inflamed eye containing infarcted retina is a situation which, in theory, is likely to cause sympathetic ophthalmitis. However, after being forced to operate on two only eyes and on a patient with bilateral diabetic retinopathy in whom the glaucomatous eye saw better than the normotensive eye we have gradually relaxed our criteria for operation, so that we operate in the presence of a good fellow eye if the eye has light perception and if the patient chooses an implant after having the dangers pointed out to him and after having been offered a quick and safe end to his pain through enucleation.

All 12 eyes drained by implants had iris neovascularisation, corneal oedema, and severe pain. Intraocular pressures on full doses of acetazolamide, glycerol, and gutt. adrenaline tartrate (Epitrate) 2% varied from 42 to 75 mmHg, while in 6 of the cases free blood was present in the anterior chambers. Visual acuity of these eyes varied from light perception only in 9 eyes through counting fingers at 2 m (1 eye) at 5 m (1 eye) to 3/60 (1 eye).

In 2 cases the underlying pathology was considered to be chronic angle closure glaucoma with secondary central retinal vein occlusion. In 5 cases vein occlusions occurred without obvious local cause, while in the remaining 5 cases iris neovascularisation was associated with grade IV diabetic retinopathy. Both patients with primary angle closure glaucoma were healthy, but of the remaining 10 cases, 9 patients had serious general disease including myocardial ischaemia in 3 cases, vascular hypertension in 1 case, and severe diabetes in 5 cases. Of the diabetics 3 had markedly elevated blood urea levels and proteinuria as a result of advanced diabetic nephropathy.

Surgical technique

Cases were prepared for operation with a combination of gutt. adrenaline tartrate 2% every 30 minutes for 2 hours before operation, acetazolamide 250 to 500 mg intravenously 1 hour before operation, and mannitol 10% solution 100 to 400 ml by slow intravenous infusion, starting 30 minutes before operation, to lower the intraocular pressure as much as possible.

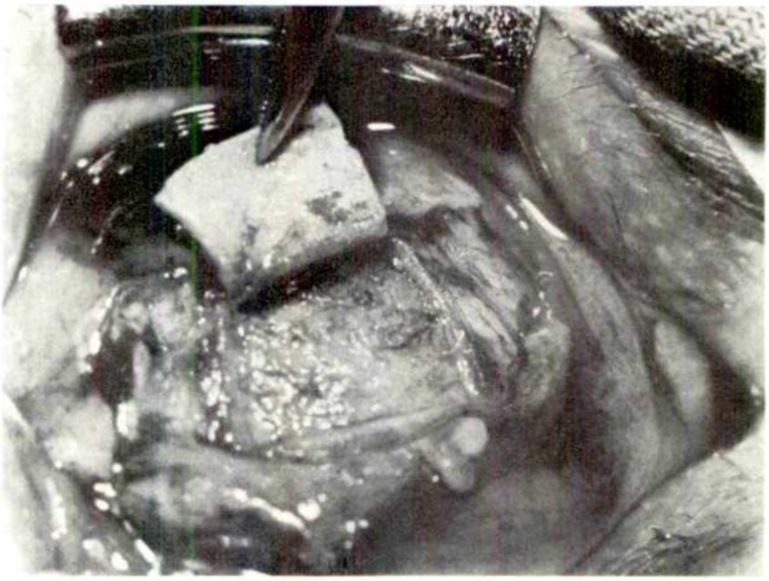

Fig. 2 *Insertion of implant. A deep lamellar scleral flap has been dissected up to the limbus (patient 8)*

Anaesthesia

General anaesthesia was preferred, but when the general condition was poor operations were done under neurolept analgesia and local injection of 2% lignocaine retrobulbarly and over the condyle of the mandible.

Dissection and placing of implants

After inserting a speculum and passing a suture beneath the superior rectus muscle near its insertion the globe was rotated so as to expose the supero-nasal or supero-temporal quadrant. The conjunctiva and Tenon's capsule were separated from the limbus and a large fornix-based flap raised and dissected posteriorly to expose the insertions of superior and medial (or lateral) rectus muscles and gain access to Tenon's space.

After cleaning sclera and cauterising all bleeding points in the exposed quadrant a large square lamellar flap of sclera was dissected up and reflected at the limbus, care being taken not to enter the anterior chamber (Fig. 2). The implant was then placed in position and the episcleral plate sutured firmly to sclera, using two anterior suture holes and interrupted mattress sutures of 7·0 silk. The next step was to cut off the tube so that the end overlapped the cornea by 2 to 3 mm (Fig. 3). The anterior chamber was entered by a circumferential limbal incision under the lamellar flap using a no. 11 Bard Parker blade and a broad or large peripheral iridectomy performed without any special precautions to prevent bleeding. The free end of the silicone tube was then inserted into the anterior chamber, and after it was arranged to lie free in the centre of the iridectomy it was firmly fastened in this position by means of a 7·0 silk suture passed around the tube, through the lamellar flap, and tied tightly so as to prevent the tube becoming displaced sideways, being withdrawn from the anterior chamber, or sliding further into the anterior chamber and touching the central corneal endothelium (Fig. 4).

Closure

After the scleral flap had been sutured into position by 4 interrupted sutures of 6·0 silk, Tenon's capsule was drawn forward over the episcleral plate of the implant and sutured to sclera near the limbus, while the conjunctiva was held in apposition to the limbus by a 7·0 silk suture at each corner of the flap. The operation was completed by injecting a mixture of gentamycin, cephalosporin, and methylprednisolone (Depot Medrol) beneath the conjunctiva away from the implant.

Postoperative management

The operated eye only was padded, and patients were mobilised the following day in spite of the presence of a hyphaema in every case.

Local medication consisted of gutt. atropin. 1%, gutt. adrenaline tartrate 2%, and gutt. dexamethason. 0·1% all given 3 times a day for 6 weeks, after

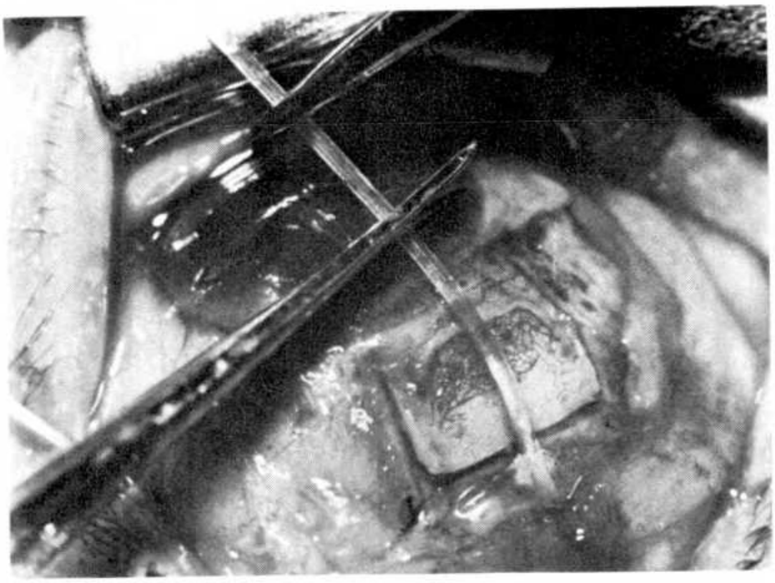

Fig. 3 *The implant has been sutured to sclera and the silicone tube laid across the eye so as to cut off the end, 2 mm inside the limbus*

which atropine and dexamethasone were stopped while adrenaline tartrate was continued in twice daily dosage until the intraocular pressure fell below 15 mmHg.

All patients received a combination of a steroid, fluphenamic acid, and colchicine to control inflammation and limit fibrosis round the implant. As many of these patients were unable to tolerate large doses of systemic steroids and others had severely reduced renal function, our usual regimen of prednisone 10 mg t.i.d., fluphenamic acid 200 mg t.i.d., and colchicine 0·25 to 0·5 mg t.i.d. for 6 weeks was modified where necessary by replacing systemic steroids by a weekly subconjunctival injection of 0·25 ml of methylprednisolone and adjusting the dose of fluphenamic acid and colchicine according to renal function.

Postoperative behaviour of intraocular pressure

After insertion of an implant the eyes remained soft for up to 3 weeks, after which the intraocular pressures rose gradually to a peak of between 35 and 60 mmHg (6 to 9 weeks after operation) and

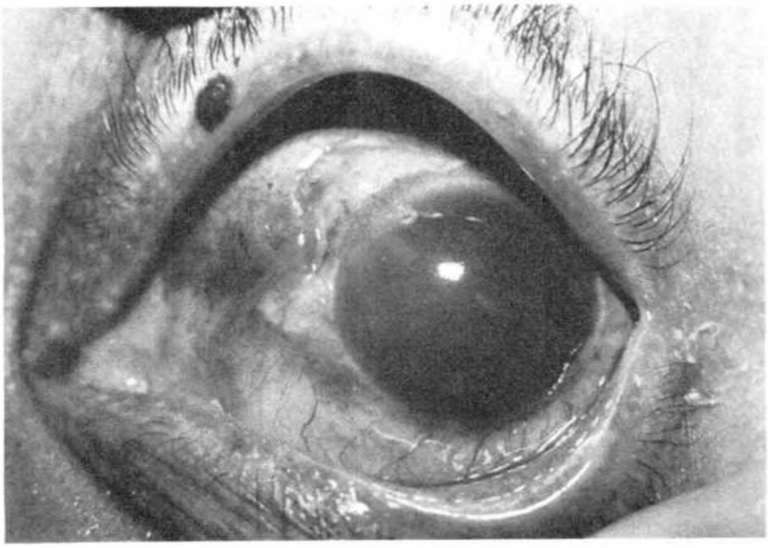

Fig. 4 *Eye of Patient 8, 7 months after operation, showing broad iridectomy and distended bleb over implant (intraocular pressure 15 mmHg on adrenaline tartrate 2% b.d.)*

Table 1 *Effect of implants on IOP*

Patient	*Sex*	*Age*	*Preop. IOP*	*Present/final IOP*	*Treatment*	*Follow-up (months)*	*Remarks*
1	Male	45	60	10–30	E	38	Late bleb thickening Second implant after 24 months Recurrent vitreous haemorrhage
2	Male	54	64	30	E	16	Iris blocked tube Second implant after 3 months Persistent low-grade iritis
3	Male	82	45	10	—	16	Eye quiet
4	Male	72	55	30	E	14	Eye quiet
5	Female	55	53	15	—	14	6/12 vision Eye quiet
6	Female	70	42	5	—	10	Bleb perforation Implant removed after 8 months Poor general state due to rheumatoid arthritis
7	Female	68	67	12	E	8	Eye quiet Died at 8 months Uraemia and diabetes
8	Female	58	75	15	E	9	Eye quiet
9	Female	42	50	18	E	9	No rubeosis Eye quiet
10	Male		70	30	E A	9	Eye quiet
11	Male	48	80	20	E	8	Ectropion uvea Eye quiet
12	Female	55	52	17	E A S	6	Eye quiet

E = Epitrate (adrenaline tartrate). A = Atropine. S = Sofradex (framycetin, dexamethasone, and gramicidin)

then fell rapidly at first and then more gradually to a stable value some 3 to 6 months after operation. The 'stable stage' pressures of 11 eyes with implants are between 10 and 20 mmHg in 6 eyes and between 20 and 30 mmHg in 5 eyes, while follow-up varies from 6 months to 38 months (Table 1).

Visual results

The visual acuity improved from 3/60 to 6/12 in one patient whose central vein occlusion was precipitated by chronic angle closure glaucoma. However, in the remaining cases, although measurable improvement did not occur, all patients but one have retained their preoperative vision so far.

Behaviour of iris neovascularisation

The abnormal neovascular formations on the iris persisted as long as the intraocular pressure was elevated, but once it fell towards normal values (below 35 mmHg) the vessels collapsed and became very inconspicuous. However, they did not disappear, for where the intraocular pressure again became elevated or if the anterior chamber became active (Table 1) they filled with blood and became obvious once more.

Early complications

The postoperative course of these eyes was characterised by a hyphaema in every case ranging from a small collection of blood that took 6 days to clear to a full hyphaema which took 3 weeks to clear. The presence of blood in these cases did not alter the treatment in any way and was not associated with severe pain or elevation of pressure.

A more serious complication was iris blocking the drainage tube. This occurred in 3 of the earlier cases and was cleared surgically in 1 while in the remaining 2 cases a second implant was inserted.

Late complications

In 1 patient with severe rheumatoid arthritis and abnormally fragile tissue the anterior chamber remained very shallow with hypotony for 8 months, after which the implant became partially exposed by breakdown of the overlying conjunctiva and was removed. The only other late complication has been a late rise in pressure associated with recurrent massive vitreous haemorrhages. This occurred 2 years after insertion of the initial implant and was treated by insertion of a second implant, which has given reasonable control of pressure up to the time of writing (14 months).

Our results can be summed up by the statement that after 14 operations carried out on 12 eyes with neovascular glaucoma all 12 eyes are pain-free and have a pressure of less than 30 mmHg without any systemic hypotensive medication.

Discussion

The use of implants to treat thombotic glaucoma is the culmination of a long series of animal experiments and clinical investigations, during which the implant technique has been extended to treat increasingly severe and complex cases of glaucoma so that a series of more than 330 operations with up to 10 years' follow-up is available for study. In spite of this experience the authors have found the treatment of neovascular glaucoma a difficult and demanding field, because, in general, the patient's state is poor, the use of steroids, fluphenamic acid, and colchicine is essential for control of bleb fibrosis, and the postoperative behaviour of these eyes is stormy. However, the ultimate results are surprisingly good, and even better results will be obtained in future now that the need for a broad iridectomy to remove iris from the vicinity of the tube is recognised. Many more cases are needed to assess the risks of sympathetic ophthalmitis and to decide the ultimate visual prognosis of these eyes. However, at present we consider that insertion of an implant with pharmacological control of bleb fibrosis is the treatment of choice for neovascular glaucoma in only eyes, in cases with bilateral predisposing disease, and where significant vision is present in the glaucomatous eye.

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Fluorescein angiography in chronic simple and low-tension glaucoma

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SUMMARY Fluorescein angiograms were performed on a group of low-tension glaucoma and chronic simple glaucoma patients with similar extent of visual field loss, under standardised conditions, to see whether differences attributable to chronic intraocular pressure elevation could be detected. There was no evidence for difference in circulation times between these two groups. There was no evidence that hypoperfusion of the peripapillary choroid contributed to optic nerve hypoperfusion. Low-tension glaucoma patients demonstrated focal sector hypoperfusion of the optic nerve in every case, while the chronic simple glaucoma patients demonstrated a wide range of optic nerve fluorescence, suggesting both focal and diffuse optic nerve head hypoperfusion. It was concluded that, while focal hypoperfusion of the optic nerve may reflect susceptible vasculature at the nerve head with or without intraocular pressure elevation, diffuse hypoperfusion suggested that prolonged intraocular pressure elevation may simultaneously affect the whole of the optic nerve head. This could be a direct effect on blood vessels or a mechanical effect with secondary vascular changes.

The hallmarks of glaucomatous disease are cupping and pallor of the optic nerve head together with visual field loss and elevated intraocular pressure (IOP). The relative importance of an elevated IOP and vascular disease of the optic nerve head in the causation of cupping of the optic nerve have yet to be determined. Optic nerve head disease in chronic glaucoma may only be the result of a direct mechanical effect of elevated IOP on the neurones or glial cells (Fuchs, 1916; Smith, 1965; Emery *et al.*, 1974; Anderson, 1975). In contrast, the glaucomatous optic nerve may reflect primary vascular or haematological disease principally affecting the optic nerve head (Drance, 1972) in a manner similar to those examples of acute anterior ischaemic optic neuropathy which are followed by an increase in volume of the optic cup (Hayreh, 1974). Finally, the glaucomatous optic nerve may be a result of vascular disease of the optic nerve secondary to an elevated IOP (Hayreh, 1970).

This paper assesses the role chronic elevation of IOP may have in the pathogenesis of glaucomatous optic nerve disease by comparing the fluorescein angiograms from eyes with similar visual field defects which were known to have either chronic simple or low-tension glaucoma.

Material and methods

The patients reported here formed part of a larger investigation utilising fluorescein angiography to study the vascular circulation of glaucomatous eyes. Cases selected for inclusion in this study fulfilled the following criteria:

(a) Visual field examination showed an arcuate scotoma, defined as a scimitar-shaped defect which extended from the blind spot to pass above or below fixation and which terminated at the horizontal meridian nasal to fixation. Patients whose visual fields revealed lesser or greater defects were not included.

(b) Glaucomatous cupping, defined as vertical cup/disc ratio of >0.5, together with any of the following: localised (asymmetrical) thinning of the neuroretinal rim, localised (asymmetrical) pallor of the neuroretinal rim, and a difference in the cup/disc ratios between the two eyes of >0.2 diameter.

(c) Fluorescein angiography and visual field

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Address for reprints: Mr R. A. Hitchings, Moorfields Eye Hospital, City Road, London, EC1V 2PD examination performed within one month of each other (usually on the same day). The technique employed for both investigations was the same in each case and has been fully reported elsewhere (Spaeth, 1975).

(d) Intraocular pressure of 22 mmHg or less, both at the time of the visual field examination and immediately following the angiogram.

(e) Angiograms of good quality with frames separated by $<1{\cdot}0$ second interval in the early phase of the angiogram allowing accurate determination both of circulation times and filling of the disc and peripapillary choroid. The angiographic technique and method used to determine circulation times have been fully described by Spaeth (1975). Angiograms with pseudofluorescence of the optic disc were rejected because of difficulties in interpretation.

The two groups of patients were: *(a)* classical chronic simple glaucoma patients with an intraocular pressure of >21 mmHg at the time of presentation; *(b)* low-tension glaucoma patients, in whom the diagnosis was confirmed by a diurnal pressure curve which documented intraocular pressures consistently <22 mmHg, together with a normal facility of aqueous outflow. Each patient with low-tension glaucoma had a neurological examination to exclude non-ocular causes for the visual field defect. No patient had suffered a period of systemic hypotension. 18 eyes with chronic simple glaucoma and 9 eyes with low-tension glaucoma filled these criteria.

Analysis of the fluorescein angiogram

While analysing the fluorescein angiograms the following criteria were checked:

1. TRANSIT TIMES

(a) Retinal transit times. The time between the first appearance of dye in the central artery and its appearance in a temporal retinal vein at, or distal to, the first major tributary.

(b) Disc transit time. The time between the first appearance of the dye in the optic disc and its appearance in superficial disc veins. The disc veins could be seen as small collector channels arising from the racemose capillary network on the optic disc (Shimizu, 1974). Identification of this 'disc circulation' could be made with certainty only in well focused angiograms, having several frames in the early part of the fluorescein 'run'. Only fluorescein angiograms where this circulation could be identified were included in this study. (The racemose capillary system is visible in the pre-arterial part of the fluorescein run and disc veins are visible in the arterial phase. Visibility of the disc veins is lost in the early venous phase of the angiogram with filling of the radial epipapillary capillaries (Shimizu, 1974) which run on to the 'surface' of the disc.)

2. FLUORESCENCE OF THE OPTIC DISC AND PERIPAPILLARY CHOROID

Disc filling was said to have occurred when dye could be seen in the superficial disc veins [*(b)*—above], although this did not correspond with the most intense or peak fluorescence of the optic disc, which occurred seconds later. Some of the optic discs had spatial filling delays lasting for two or more frames before peak fluorescence was achieved; this was designated *delayed fluorescence* of (part of) the optic disc. Other patients showed areas of the disc which had not reached peak fluorescence by the late venous phase of the angiogram; this was designated *hypofluorescence* of the optic disc. We found that hypofluorescence occurred in three different patterns which will be described below. Hypofluorescence was thought to represent hypoperfusion of the optic disc. Hypofluorescence characteristically persisted for upwards of one minute until obliterated by late diffuse disc fluorescence. Filling of the peripapillary choroid was said to have occurred when the outline of the choroidal vessels was replaced by a diffuse choroidal fluorescence.

Delayed filling of the peripapillary choroid was said to have occurred when an area of the peripapillary choroid showed persistence of the choroidal vessel pattern for two or more frames after another area had already filled. No example of delayed filling of the peripapillary choroid persisting until the late venous phase (theoretical *hypofluorescence* of the peripapillary choroid) as described by Hayreh (1974) was seen.

The optic disc was divided into optic cup and neuroretinal rim, so that 3 concentric zones of cup, rim, and peripapillary choroid were identified on the angiogram and corresponding areas in these zones of normal, delayed and reduced fluorescence could be ascertained. The following were looked for: (1) Areas of disc hypofluorescence; (2) areas of delayed peripapillary choroidal filling occurring next to areas of disc hypofluorescence.

Results

Intraocular pressures and systemic blood pressure at the time of the angiogram are listed in Tables 1 and 2 respectively, retinal and disc transit times are listed in Tables 3 and 4 respectively. There was no major difference between the 2 groups for any of these parameters.

Three patterns of hypofluorescence of the optic disc

Table 1 *Intraocular pressure at the time of the angiogram*

	Mean IOP (mmHg)	*Range (mmHg)*	*Median (mmHg)*
Chronic simple glaucoma	17·0	11–22	18·0
Low-tension glaucoma	18·0	14–22	18·0

Table 2 *Blood pressure at the time of the angiogram*

	Mean BP (mmHg)	*Range (mmHg)*	*Median (mmHg)*
Chronic simple glaucoma	127/79	96/63–160/90	120/80
Low-tension glaucoma	130/82	120/70–154/90	122/80

Table 3 *Retinal transit times*

	Mean (sec)	*Range (sec)*	*Median (sec)*
Chronic simple glaucoma	1·7	1·1–4·4	2·0
Low-tension glaucoma	1·6	0·4–2·6	1·4
Normal subjects	2·0*		

*Figures from Spaeth, 1975

Table 4 *Disc transit times*

	Mean (sec)	*Range (sec)*	*Median (sec)*
Chronic simple glaucoma	1·6	0·7–61	1·2
Low-tension glaucoma	1·0	0·3–2·6	0·7
Normal subjects	1·4*		

*Figures from Spaeth, 1975

could be seen. It must be emphasised that these patterns of optic disc hypofluorescence will only be seen on well-focused angiograms. These patterns have been called sector, patchy, and extensive. *Sector* hypofluorescence referred to a wedge of hypofluorescence extending from the outer edge of the neuroretinal rim towards the centre of the disc involving the adjacent part of the optic cup, the remainder of the optic disc appearing to fluoresce in a normal fashion (Fig. 1). *Patchy* hypofluorescence described optic discs with two or more areas of neuroretinal rim hypofluorescence separated by apparently normally fluorescing areas and associated with variable hypofluorescence of the optic cup (Fig. 2). *Extensive* hypofluorescence referred to a single area of hypoperfusion of the neuroretinal rim together with hypofluorescence of the entire optic cup (Figs. 3 and 4). The incidence of the various patterns of optic disc hypoperfusion in the 2 groups may be seen in Table 5. Whereas 'normal' fluorescence (Fig. 5) and all 3 patterns of hypofluorescence were seen in the eyes with chronic simple glaucoma, sector hypofluorescence only was seen in patients with low-tension glaucoma.

The results of comparing areas of delayed peripapillary choroidal filling with areas of optic disc hypofluorescence may be seen in Table 6. No difference was apparent between the 2 groups. Delayed filling of the peripapillary choroid was not preferentially sited adjacent to hypofluorescent areas of the neuroretinal rim.

The peripapillary choroidal filling delay did not persist for more than 3·5 seconds in any case.

Table 5 *Hypofluorescence of the optic disc*

	Pattern of hypofluorescence	*No. of eyes*
1. Chronic simple glaucoma	Sector hypofluorescence	4
	Patchy hypofluorescence	4
	Extensive hypofluorescence	9
	Normally fluorescing disc	1
2. Low-tension glaucoma	Sector hypofluorescence	9

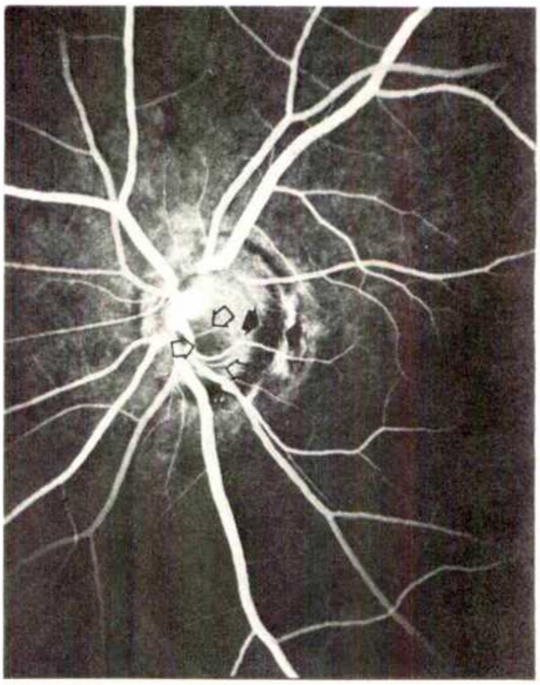

Fig. 1 SECTOR HYPOFLUORESCENCE *of the optic disc, seen in the inferotemporal quadrant* (outlined by hollow arrows). *Elsewhere the optic disc appears to fluoresce normally. Care must be taken to distinguish hypofluorescence of the optic disc from 'masking' caused by peripapillary pigment* (solid arrows)

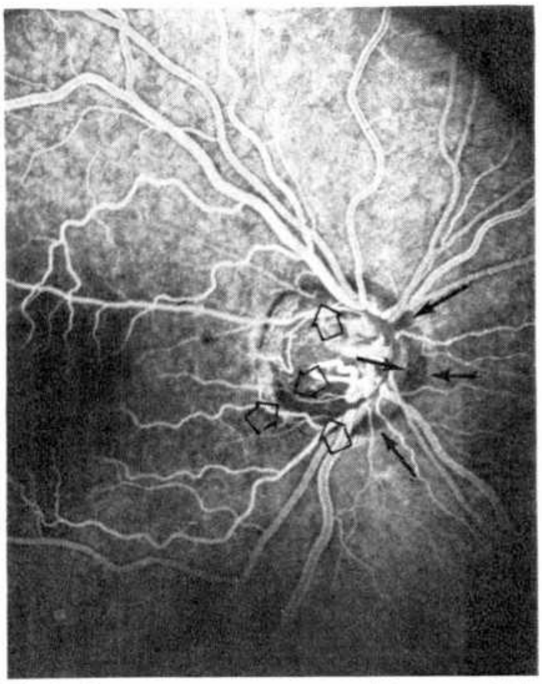

Fig. 2 PATCHY HYPOFLUORESCENCE *of the neuroretinal rim* (hollow arrows) *associated with hypofluorescence of part of the optic cup. Hypofluorescence from peripapillary pigment is also seen* (solid arrows)

Discussion

This investigation reports on the use of fluorescein angiography to contrast the papillary and peripapillary circulations in 2 groups of glaucoma patients. For the purposes of discussion it should be emphasised that the 2 groups were similar in every respect including the type of field defect, the presence of glaucomatous cupping, and intraocular pressure ≤22 mmHg at the time of examination. The factor which separated the 2 groups was a total lack of history of raised pressure in those eyes designated 'low-tension glaucoma', while in the eyes of the other group there was a well-documented history of long-standing elevation of IOP. Furthermore, the presence of normal tonographic values in the eyes diagnosed as low-tension glaucoma suggested that they were not, in fact, cases of 'burnt out' glaucoma. It was felt that any differences seen in the circulations studied would therefore be attributable to the only known difference between these 2 groups of patients, namely, that the group designated chronic simple glaucoma had had well-documented elevation in intraocular pressure.

Table 6 *Correlation between delayed choroidal filling and disc hypofluorescence*

	Disc hypofluorescence with adjacent choroidal filling delay (ACFD)	*Disc hypofluorescence without ACFD*	*No ACFD*
1. Chronic simple glaucoma	7 eyes	7 eyes	4 eyes (1 with circumpapillary choroidal atrophy)
2. Low-tension glaucoma	3 eyes	5 eyes	1 eye

Conditions of study were standardised as far as possible. Care was taken to ensure that intraocular pressures were within normal levels as it is known that abnormally high intraocular tensions may induce a change in the fluorescein angiogram that disappears when the IOP returns to normal (Best *et al.*, 1972; Spaeth, 1975). Similarly, care was taken to ensure that intraocular pressure was not elevated at the time of the visual field examination, as this might have affected the nature of the scotoma (Gafner and Goldmann, 1955). Repeat angiographic studies had shown that circulation times and filling patterns were reproducible (Spaeth, 1975).

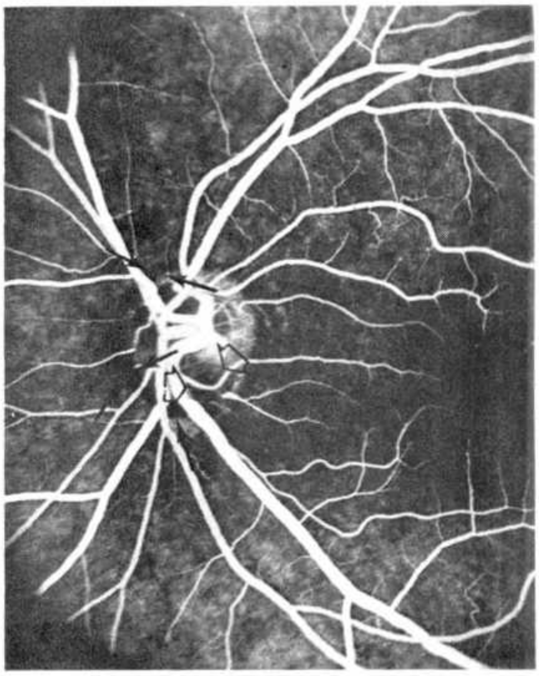

Fig. 3 EXTENSIVE HYPOFLUORESCENCE *of the optic cup togeether with localised hypofluorescence of the neuroretinal rim* (hollow arrows). *Hypofluorescence from peripapillary pigment is also seen* (solid arrows)

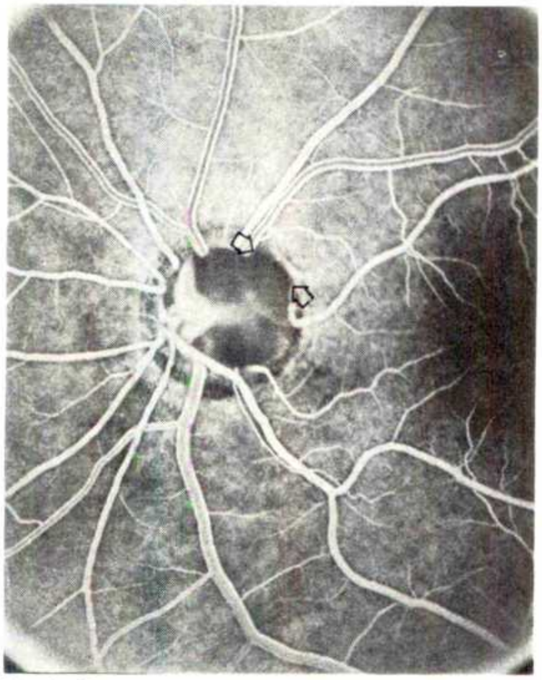

Fig. 4 EXTENSIVE HYPOFLUORESCENCE *of the optic cup together with localised hypofluorescence of the neuroretinal rim* (hollow arrows). *Hypofluorescence from peripapillary pigment is also seen* (solid arrows)

The laminar and prelaminar regions of the disc are thought by some to receive a portion of their blood supply from the adjacent peripapillary choroid on the basis of anatomical (Hayreh, 1969; Henkind and Levitsky, 1969; Francois and Neetens, 1972; Ernest, 1975), and fluorescein studies (Ernest and Potts, 1968; Hayreh, 1970; Best *et al.*, 1972). Poor autoregulation of choroidal blood flow may render the peripapillary choroidal circulation more susceptible to elevated intraocular pressures (Alm and Bill, 1973) when the blood flow to the optic disc would be diminished. Some observational support for this hypothesis has been provided by Hayreh (1974), who noted so-called peripapillary choroidal hypofluorescence, later reversing to delayed peripapillary fluorescence, in the early stages of anterior ischaemic optic neuropathy. Hayreh (1974) suggested that a similar sequence of events was the cause of optic nerve hypoperfusion and cupping. If this sequence of events was responsible for optic disc ischaemia in glaucomatous eyes, areas of focal disc hypoperfusion, visible as hypofluorescence on fluorescein angiography, should lie adjacent to regions of delayed peripapillary choroidal filling, providing these regions do not undergo spatial variation with time.

In studies reported elsewhere (Hitchings and Spaeth, 1976; Spaeth, 1975) the authors concluded that areas of peripapillary filling delay were remarkably constant in shape and site during observational periods of up to 4 years in duration.

Areas of peripapillary choroidal filling delay did not persist for more than 3·5 seconds. This delay was no greater than has been found in the normal population (Spaeth, 1975). These areas of filling delay were *not* found most frequently adjacent to areas of neuroretinal rim hypoperfusion, nor was there any difference between the 2 groups of patients. There was no evidence that focal peripapillary hypoperfusion played any part in the pathogenesis of disc hypofluorescence in either of the 2 groups of patients in this study.

There was no evidence for any difference in circulation times between the 2 groups of patients. Nor was there systemic hypotension in the patients with low-tension glaucoma. No patient had had an episode of acute systemic hypotension that might have precipitated the field loss (Drance, 1972). These findings are slightly surprising in view of the reports that patients with low-tension glaucoma have a higher incidence of haematological, biochemical, and vascular disease and a lower systemic blood pressure than patients with chronic simple

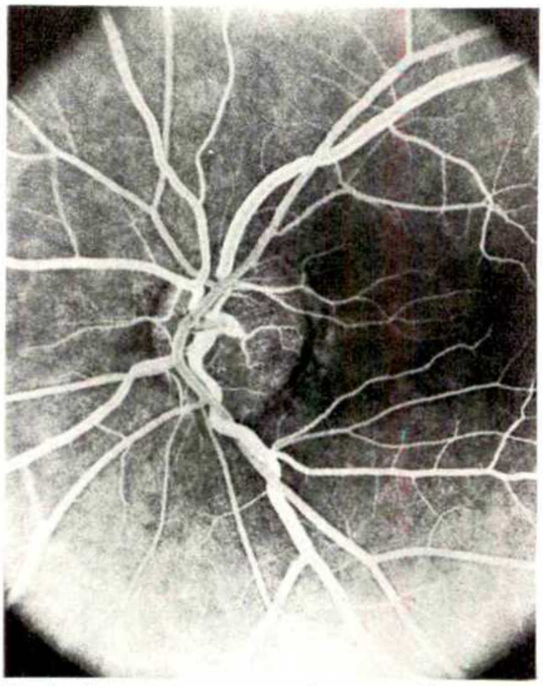

Fig. 5 NORMAL FLUORESCENCE *in an eye with an upper arcuate scotoma*

glaucoma (Drance, 1972; Leighton and Phillips, 1972; Winder *et al.*, 1974). There may be similarity between patients reported here and those of Boghen and Glaser (1975), who noted that in patients with acute ischaemic optic neuropathy the incidence of vascular and haematological disease was similar to that occurring in an age and sex matched group of normal subjects.

Hypofluorescence of the neuroretinal rim rather than hypofluorescence of the optic cup has been found to correspond with areas of field loss (Spaeth, 1975; Hitchings and Spaeth, 1976). These angiographic pictures of papillary hypofluorescence are reproducible, they persist despite long-term 'control' of intraocular pressure, and do not seem to 'improve' with time (Spaeth, 1975). In this series the arcuate field defect was associated with hypofluorescence of the neuroretinal rim in all bar one patient (Fig. 5). This patient, however, had 'normal' fluorescence of the optic disc, and it must be assumed that at this stage no changes in the vascular network of the optic nerve, detectable by optic disc angiography, had occurred.

Four patients had small patches of hypofluorescence on the neuroretinal rim in areas *not* corresponding with the visual field defect. Repeat angiograms confirmed these defects. It is likely that these hypofluorescent areas represent hypoperfusion and reflect reduced neuronal function. The resultant field defects must have been too small to be noticed by the patient with the method of Goldmann field testing employed in this study (Spaeth, 1975).

The 2 groups of patients differed in that only those patients in the group labelled 'chronic simple glaucoma' were known to have had chronic elevation of intraocular pressure. The fluorescein angiograms differed in that all patients with low-tension glaucoma showed sector hypofluorescence, while a more varied pattern, including sector hypofluorescence was seen in the eyes that had chronic simple glaucoma. Begg *et al.* (1972) also noted sector hypofluorescence in a group of 10 patients, each with an arcuate scotoma, 3 of whom were diagnosed as low-tension glaucoma. Sector hypofluorescence is explained by non-perfusion of the radial centrepetal prelaminar arteries, described by Hayreh (1970). In some individuals these vessels would appear particularly vulnerable, *localised* non-perfusion occurring in the absence of elevated intraocular pressure. The resultant glaucomatous cupping with field loss is diagnosed as low-tension glaucoma. Similar vascular non-perfusion occurs in some patients with chronic simple glaucoma. However, eyes with chronic simple glaucoma may demonstrate a far greater degree of papillary hypofluorescence (13 out of 18 in this series). This suggests chronic elevation of intraocular pressure may affect blood vessels over the whole area of the disc, either directly, or indirectly following loss of neurones or glia.

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British Journal of Ophthalmology, 1977, **61**, 133–134

A note on stray light in the Tübingen perimeter

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SUMMARY Measurements were made of the relative intensity of light scattered in the neighbourhood of the large and small targets on the Tübingen perimeter. Two target intensities were studied. The scattered light fraction ranged from 0·1 to 25%, and its effect was detected more readily by young than by older observers.

Most perimeters provide visual test stimuli by reflection at a painted surface. In these circumstances the definition of the stimulus, let alone of the retinal image, becomes a problem because of stray light. This is easily seen in bowl perimeters, such as those designed by Goldmann and by Harms, when, for example, a target of 10 asb intensity is projected on a background of zero intensity. A wide halo is seen to surround the target, and to become even more noticeable in non-foveal vision, once the eye begins to adapt to the dark.

Although stray light in the eye has understandably received much attention (Ranke, 1954; Wolf and Gardiner, 1965), we have not come across any study of the significance of the problem from the clinical point of view. As our attention to the question was attracted by a difficulty in interpreting the results of static perimetry in a series of clinical scotopic tests, we made the following measurements.

Methods

A Tübingen perimeter (Oculus) was used. Five observers with normal vision and ranging in age from 23 to 53 years were asked to make foveal matches between the luminances of the target and its immediate neighbourhood.

For this purpose they were provided with clean, calibrated neutral density filters. One edge of the filter or filter combination was made to overlie the target, the total density being adjusted till a match was obtained with a neighbouring area. Each measurement was made three times on three different days. The variables included stimulus intensity (100 and 1000 asb, as lower values yielded nothing of significance) and angular diameters of 10′ and 104′.

Results

The averaged values and their standard deviations are shown in Fig. 1. Target luminance is plotted along the abscissa and the filter density needed to equate target and surround luminance along the ordinate. Expressed in arithmetical units, the apparent brightness ratio ranges from 0·1 to 25%—that is, from the barely to very significant. In general, this ratio varies only with the smaller of the two targets, being more important at the lower intensity.

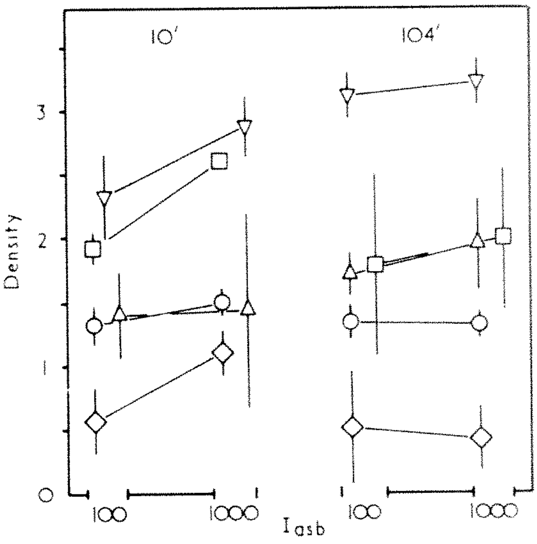

Fig. 1 *Abscissa: target luminance; ordinate: filter density needed for a visual match between target and surrounding area. The different symbols refer to different observers*

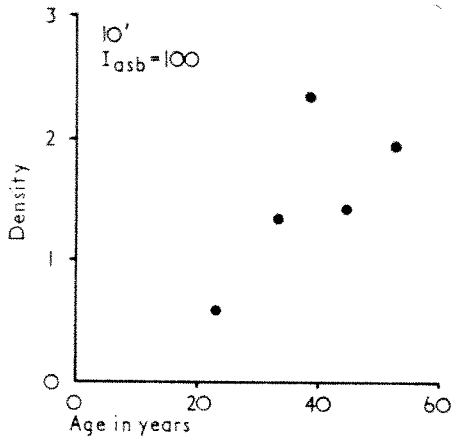

Fig. 2 *Filter density (cf. Fig. 1) as a function of the observer's age*

The variation for the large target is statistically non-significant. Application of the χ^2 test to the 10′ data shows them to be significant at a level of $P<0{\cdot}001$. Even if the data represented with squares are arbitarily omitted in order that we may establish whether their small error decisively biases the whole result, a significance at $P<0{\cdot}01$ is still obtained. The various symbols represent the various observers, and Fig. 2 shows with data taken from Fig. 1, as shown in the inset, that there is some correlation with the age of the observer. The numbers are too small for too much emphasis to be put on this point.

Conclusion

The data show that stray light can cause an increase in the apparent size of a perimetric test target. The effect is more likely to play a role in younger eyes. At target intensities near the threshold the stray light may be below threshold and may be virtually undetected except after dark adaptation. At very high intensities intraocular scatter and glare may render it unnoticeable. However, at intermediate intensities it is clearly measureable and can act by reducing the apparent extent and depth of scotomata. It is easy to envisage situations wherein stray light may offer a more powerful stimulus than does the target owing to the integrative properties of the retinal periphery. Instrument design and observer and patient variability seem to exclude the possibility of applying any but the crudest correction to measurements obtained when extraneous stray light plays a role. It is evident that the problem can be circumvented with the use of self-luminous tests—e.g., in the shape of light-emitting diodes.

Our thanks are due to Sister Elizabeth Firkins, Miss G. M. Villermet, and Miss Jill Walker, who willingly helped as observers.

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Cataract in childhood: photographic methods in assessment

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SUMMARY The slit-lamp examination of the child's lens with cataract can yield useful prognostic signs, especially when this is supplemented by slit-image photography and measurement. A normal lens size for the subject's age is a good prognostic sign and is usually associated with a static cataract or with very slow deterioration in a developmental cataract. A small lens and absence of the anterior subcapsular clear zone are each associated with progressive cataract. Nuclear lamellar cataracts are shown to become smaller in diameter with time, which favours medical treatment with mydriasis.

The technique of quantitative slit-image photography of the lens (Fig. 1) (Brown, 1972a, b) provides information on the dimensions of the lens, including sagittal width and radius of curvature of the surfaces and of dimensions and situation of the cataract. This information is not easily obtained by any other technique, and the photographs have also the advantage of providing a permanent record with which to compare future examinations. A number of features in the photographs have prognostic value, in particular the observation of the anterior subcapsular clear zone and of lens size. This technique has also provided new information on normal lens growth and on the natural history of cataracts.

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Lens growth

The lens grows at a steady rate throughout life, at least between the ages of 10 and 80 (Fig. 2) (Francois, 1959; Brown and Tripathi, 1974), but there are insufficient data below the age of 10 to say whether the growth rate is any different then. The growth is mainly cortical, and there is very little change in the width of the nucleus with age (Fig. 2), when the limit

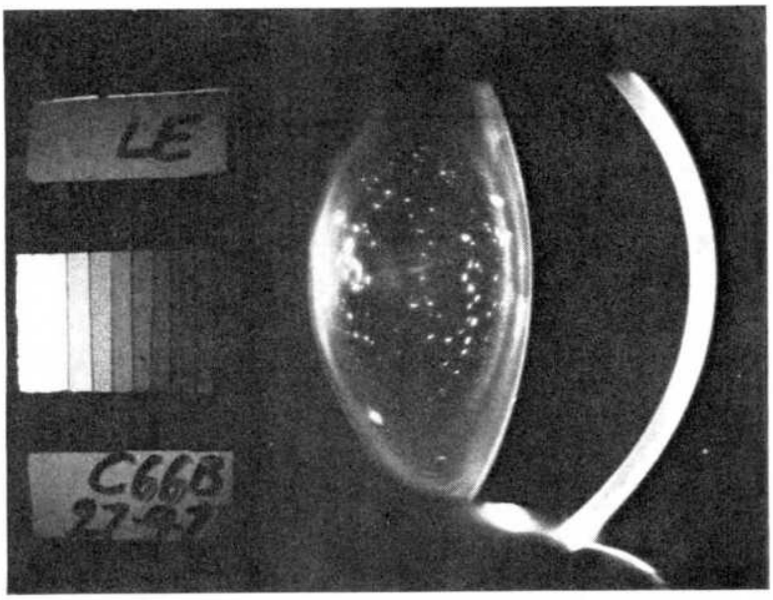

Fig. 1 *Slit-image photograph of the lens of a year-old girl showing developmental cataract*

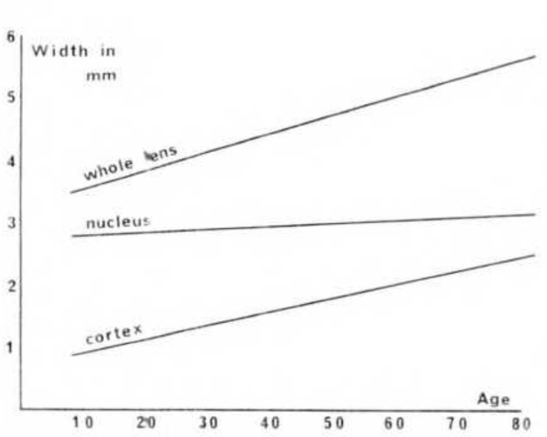

Fig. 2 *Graph showing the growth in sagittal width of the normal lens with age*

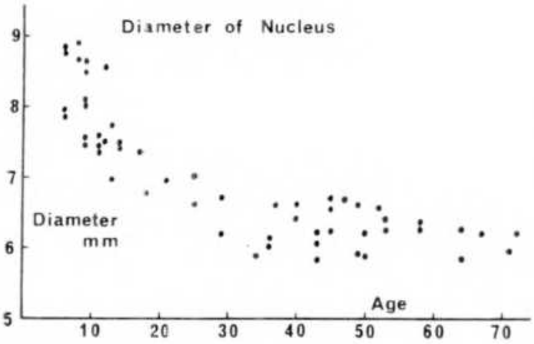

Fig. 3 *Graph showing the reduction in equatorial diameter of the nucleus with age*

of the nucleus is defined by the sudden change in optical density which is seen in the slit-image pictures. While the width of the nucleus remains nearly constant, the equatorial diameter is actually becoming less with age (Fig. 3) and is most rapid in childhood. This has an effect on the size of nuclear cataracts, causing them to become smaller with age.

A small lens size for the subject's age is seen in lenses developing certain forms of cataract, in particular progressive anterior or posterior subcapsular cataract (Brown and Tripathi, 1974). A normal lens size is seen in static cataracts such as congenital nuclear cataracts and congenital anterior and posterior polar opacities. Thus, a normal lens size in an eye with cataract is a good prognostic sign. This is particularly valuable in developmental cataracts, which are discussed separately below.

A small lens size can also be seen following trauma (Fig. 4) either blunt or perforating. This is commonly seen in those lenses which have been examined within a few days of the trauma. The size recovers to normal in those lenses in which recovery of growth takes place (Brown, 1976). In these lenses the opacity remains static in size and sinks into the lens with time. The lenses which fail to recover to normal size are liable to deteriorate to mature cataract, which in children can be a very rapid process reaching maturity within a few weeks.

Lens curvature

The radius of curvature of the lens surfaces is easily measured from the slit-image pictures (Brown, 1973) but is very difficult to assess with the slit lamp alone.

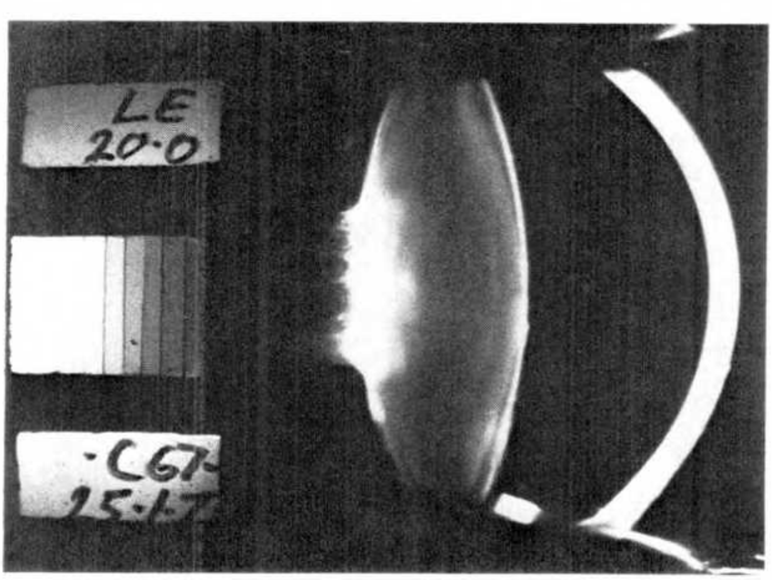

Fig. 4 *A child's lens affected by non-perforating trauma showing small size with flattening of the posterior surface*

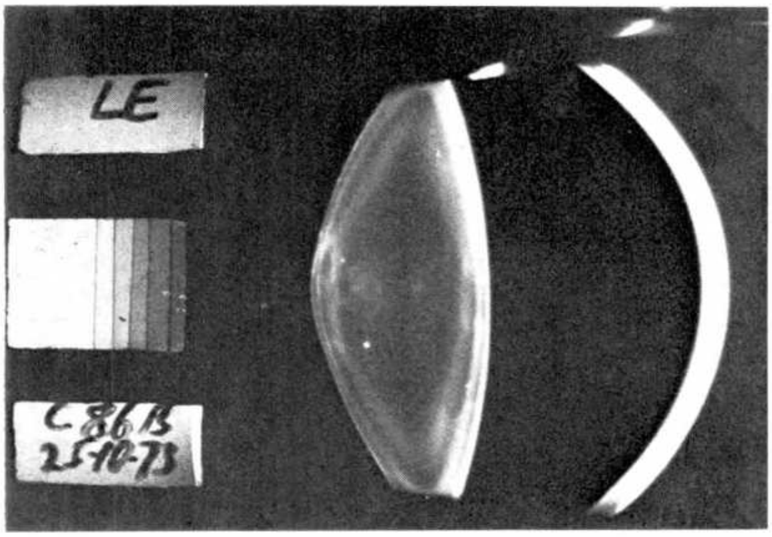

Fig. 5 *The lens of a 14-year-old child showing posterior lenticonus*

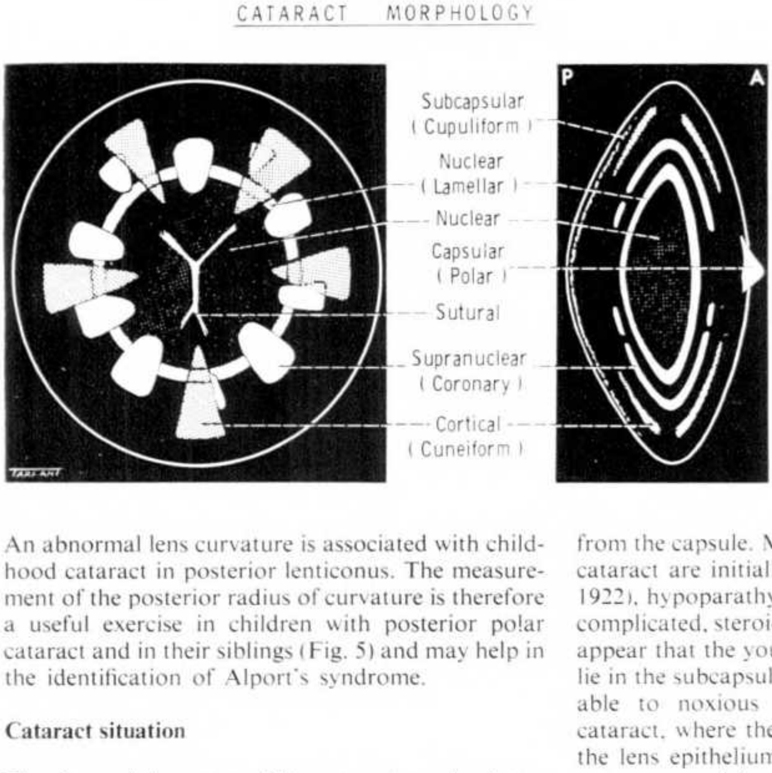

Fig. 6 *The morphological classification of cataract*

An abnormal lens curvature is associated with childhood cataract in posterior lenticonus. The measurement of the posterior radius of curvature is therefore a useful exercise in children with posterior polar cataract and in their siblings (Fig. 5) and may help in the identification of Alport's syndrome.

Cataract situation

The site and character of the cataract can be determined quite well by the clinical use of the slit lamp, which is sufficient for assigning the cataract to one of the various morphological groups of cataract (Fig. 6). Slit-image photography is important in defining the exact depth of the cataract, as measured from the capsule. Many forms of acquired childhood cataract are initially subcapsular—traumatic (Vogt, 1922), hypoparathyroid (Goldmann, 1929), diabetic, complicated, steroid, and radiation induced. It would appear that the youngest nucleated lens fibres which lie in the subcapsular clear zone are the most vulnerable to noxious influences, except in radiation cataract, where the fault appears to be primarily in the lens epithelium. When the noxious influence is not severe and is present for a limited time, the lens recovers normal growth and the opacities are seen to sink into the lens (Fig. 7). The rate at which the opacities sink in is actually faster than the lens is growing, which implies that the lens is undergoing central compression while growing by surface

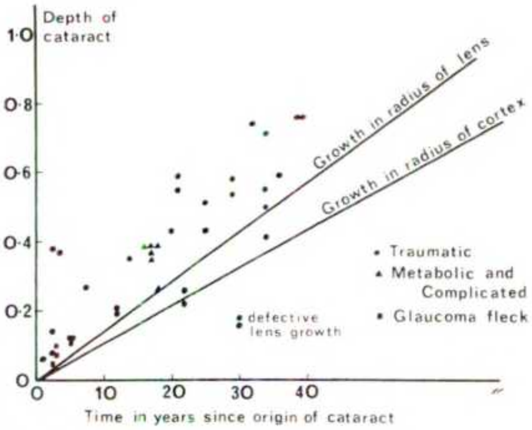

Fig. 7 *Graph showing the depth of lens opacities compared with the rate of growth of the lens*

accretion. The rate of movements is greater nearer the surface (Brown, 1976). The compression effect appears to be largely a cortical phenomenon, and cataracts never sink into the nucleus (Nordmann, personal communication), which I confirm.

Cataract size

STATIC CATARACTS

Cataracts due to an external influence such as trauma or metabolic disturbance which is short-acting tend to remain constant in size, though they do change in position as described above. Congenital cataracts, which are necessarily nuclear, since there is no cortex present at birth, are usually regarded as static but now may have to be considered as shrinking cataracts.

INCREASING CATARACTS

A cataract may increase by (i) the laying down of new lens fibres, some of which are opaque at the time of formation, as in developmental cataracts; (ii) the spread of the cataract into previously clear lens fibres, which is seen typically in senile cuneiform cataract and in children with severe traumatic cataract and in the final stage of maturation of developmental or complicated cataract; and (iii) the laying down of granular material in the subcapsular clear zone by a lens which has lost the ability for normal growth, which is seen in complicated cataract, steroid cataract, and radiation cataract, and implies the production of defective material by a diseased epithelium which has ceased normal mitosis (Brown and Tripathi, 1974). These lenses are commonly small for the subject's age. Slit-image photography is useful in identifying progressive cataract, particularly in measuring lens size and in recording the state of the anterior subcapsular clear zone. Attention has already been directed to the loss of the clear zone (Brown and Tripathi, 1974), which signifies a progressive cataract, and it is also seen in developmental cataracts which have changed from the gradual addition of new opacities to a more rapid form of deterioration.

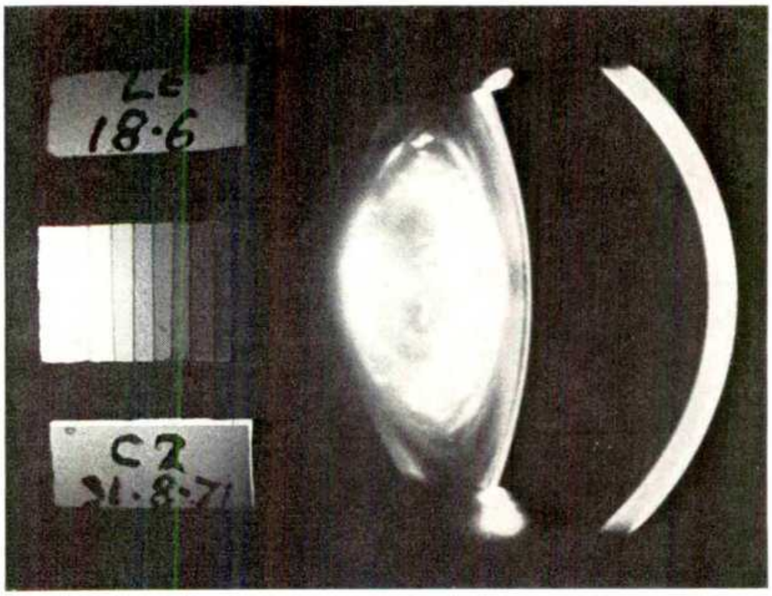

Fig. 8 *A congenital lamellar cataract in a girl aged 9*

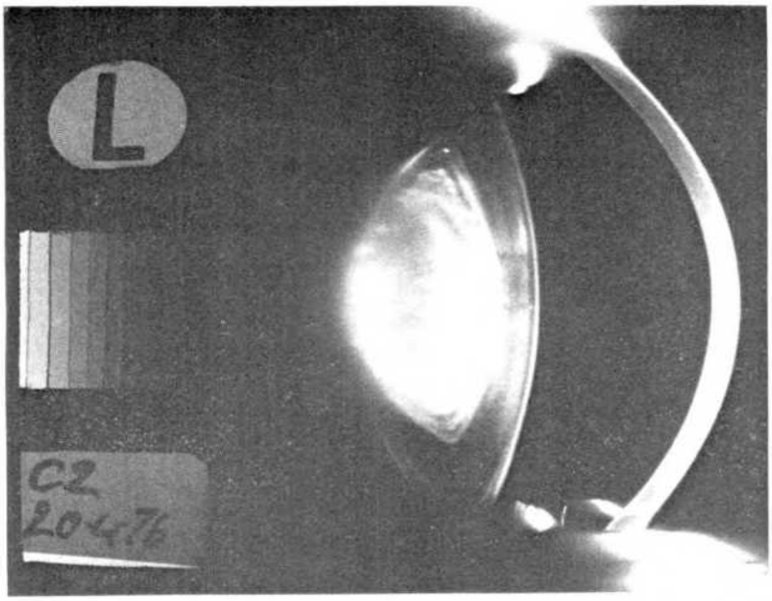

Fig. 9 *The same eye as in Fig. 8 at the age of 14. (The other eye had a cataract extraction and is amblyopic)*

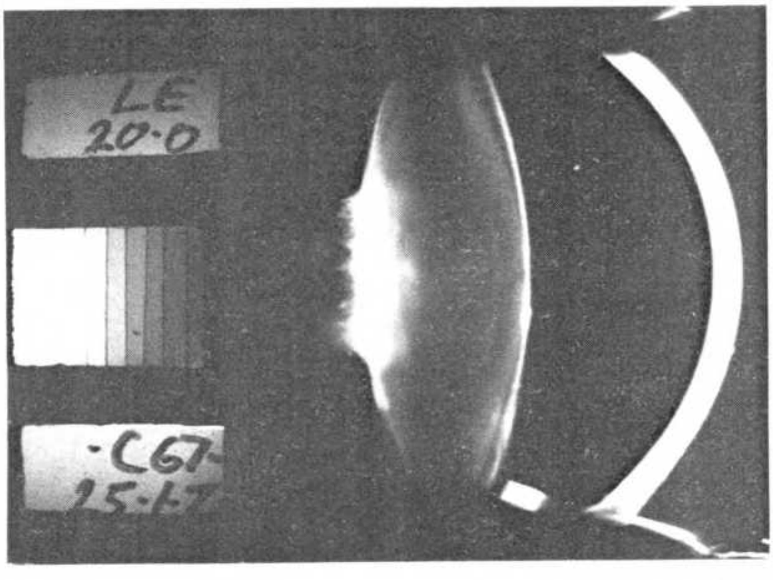

Fig. 10 *A developmental cataract which has reached the stage of rapid deterioration with loss of the anterior subcapsular clear zone*

SHRINKING CATARACTS

After the correction of an acute metabolic disturbance causing cataract, such as diabetes, there is some improvement in lens clarity and reduction in lens swelling, but no true reduction in the size of the cataract. A true reduction in cataract size probably occurs regularly in congenital nuclear cataracts, which was first suggested by the observation (Fig. 3) that the equatorial diameter of the nucleus becomes less with age. Partial confirmation has been obtained from two families with hereditary nuclear cataract, which is seen to be smaller the older the individual. Reliable confirmation (Figs. 8 and 9) is now to hand in a single lens, which has had the longest follow-up (5 years) and in which the cataract is measurably shrunken during the period of observation.

Some specific types of cataract

CONGENITAL NUCLEAR CATARACTS

The classical lamellar cataracts become compressed with time so that the affected lamella becomes thinner and smaller in diameter. The situation is only one of deterioration when developmental opacities are superadded. A clear cortex, clear subcapsular clear zone, and normal lens size should be sought as good prognostic signs. Since these cataracts commonly improve with time, medical treatment with mydriatics should be preferred unless the diameter of the cataract is initially as large as the dilated pupil.

POLAR CATARACTS

These may be flat discs or conoid (pyramidal) projections from the poles which are present from birth. These cataracts commonly change little with time. As the lens grows, further discs of opacities are commonly deposited beneath the polar opacity; they do not interfere further with vision except when their diameter is greater, and this does sometimes occur to the extent of needing extraction.

DEVELOPMENTAL CATARACTS

These hereditarily determined cataracts (Fig. 1) are commonly represented at birth by a nuclear cataract to which are gradually added punctate opacities and later coronary opacities with the laying down of a mixture of clear lens fibres and opaque fibres as the lens grows. This results in a very gradual deterioration, but may take a sudden change for the worse with failure of the subcapsular clear zone and posterior subcapsular cataract (Fig. 10). Most patients will not need a cataract extraction until adult life. The lens size is normal for the subject's age except in those lenses which are deteriorating rapidly which are small for the subject's age.

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British Journal of Ophthalmology, 1977, **61**, 141-147

Senile disciform macular degeneration in the second eye

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SUMMARY Development of senile disciform degeneration in the second eye was studied in a group of 104 patients over a period of up to five years. 12 to 15% of these patients develop disciform degeneration in the other eye each year. Patients with large and confluent drusen, especially if combined with accumulation of dye on fluorescein angiogram, were at greatest risk of developing disciform degeneration in the second eye.

Disciform macular degeneration is characterised by elevation of the pigment epithelium and retina by blood, serous fluid, and invasion of the subpigment epithelial space by fibrovascular tissue arising from the choroid. Drusen were first described by Donders (1885), but it was not until 1940 that they were recognised as a predisposing cause of disciform detachment of the macula (Gifford and Cushman, 1940). Subsequent experience has confirmed this association, so that now it is generally acknowledged that senile disciform macular degeneration occurs as a result of pre-existing changes in Bruch's membrane and the pigment epithelium.

These changes may be the result of a genetically determined disorder (Gass, 1973) or of age alone, but the nature of the changes and the manner by which they induce the disciform response have yet to be identified precisely. With increasing age Bruch's membrane becomes thicker (Hogan, 1967; Hogan *et al.*, 1971). Collagen fibres become electron dense, and irregularly banded structures appear which may be the result of degenerating collagen (Hogan *et al.*, 1971). The elastic zone becomes basophilic, the elastic fibres increase in electron density, and needle-like crystals are deposited within the fibres. Accompanying the fibre changes there is deposition of PAS-positive granular, vesicular, and filamentary material in the matrix of the inner collagen layer at first and later in the elastic zone. This material resembles the contents of pigment epithelial phagosomes, and the suggestion has been made that it consists of discharged phagosomal material (Hogan *et al.*, 1971). It has also been inferred that drusen were formed by accumulation of this material between the inner collagen layer of Bruch's membrane and the pigment epithelial basement membrane. This material probably forms the linear deposits described by Sarks (1973) which form a patchy and then continuous layer on the inner surface of Bruch's membrane.

If Bruch's membrane acts as a physical barrier to blood vessel growth, the degeneration of fibres and the distortion of fibres by accumulation of abnormal material within Bruch's membrane may allow vascular incursion into the subpigment epithelial space. Blood vessel growth may be stimulated by outer retinal ischaemia if the thickened membrane acts as a diffusion barrier. Furthermore, the presence of macrophages on the inner surface of Bruch's membrane, as described by Sarks (1976), may also stimulate blood vessel growth.

It is also relevant that penetration of Bruch's membrane by choroid vessels is common in the eyes of the elderly, being multifocal and occurring throughout the fundus (Brown, 1940; Riechling and Klemens, 1940; Friedman *et al.*, 1963), whereas recognisable disciform lesions are usually in the macular region and appear to arise from a single vascular source.

From the clinical standpoint limited studies have been undertaken concerning the risk of visual loss of an eye with drusen (Teeters and Bird, 1973; Gass, 1973; Chandra *et al.*, 1974). The exact prognostic significance of the type and number of drusen has not yet been defined, though Gass (1973) and Chandra and co-workers (1974) implied that a greater number of drusen denoted worse prognosis. Other poor prognostic signs have been suggested, including rapid increase in the number of drusen, extensive associated pigment epithelial changes, and disciform degeneration in the other eye (Gass, 1973).

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In the first part of this paper we record the incidence of second eye involvement in a group of patients with unilateral senile disciform macular degeneration who have been observed for periods varying between 1 and 5 years. In the second study reported a qualitative and quantitative assessment of predisposing changes was made, and an attempt was made to identify the type of change which put a patient at high risk of developing a lesion in the second eye.

I. INCIDENCE

Materials and methods

All patients between the ages of 60 and 69 who presented initially to Moorfields Eye Hospital with visual loss due to senile disciform macular degeneration and were seen in the retinal diagnostic department from 1970 until the end of 1974 were reviewed. A large number of patients referred from other hospitals and those over 69 were not included because of difficulties of follow-up.

In our group there were 172 patients. Of these, 104 had a disciform lesion in one eye only at the time of presentation and had been followed up for at least one year. All patients with a disciform lesion had serous elevation of the retina and the pigment epithelium and subretinal blood vessels were recognised on fluorescein angiography.

Results

Twenty-nine patients developed a disciform lesion in the second eye during the period of follow-up.

The results were analysed in two ways—in respect of length of follow-up and in respect of annual risk in completed years of observation.

I. PATIENT RESULTS

During the first year of follow-up 9 (9·8%) of the 104 patients developed a disciform lesion in the other eye. Of these, 74 were followed up for 2 years, and 18 (19%) developed disciform degeneration in the fellow eye during this period. The figures for incidence of involvement of the second eye for those followed up for 3 years was 17 of 53 (30%), for 4 years was 11 of 23 (48%), and for 5 years, 5 of 11 (45%) (Fig. 1).

II. YEARLY RESULTS

Of the 34 patients 5 (15%) followed up in 1972 developed a disciform lesion in the other eye. The incidence for 1973 was 6 of 49 patients (12%) and for 1974, 12 of 78 patients (15%) (Fig. 2).

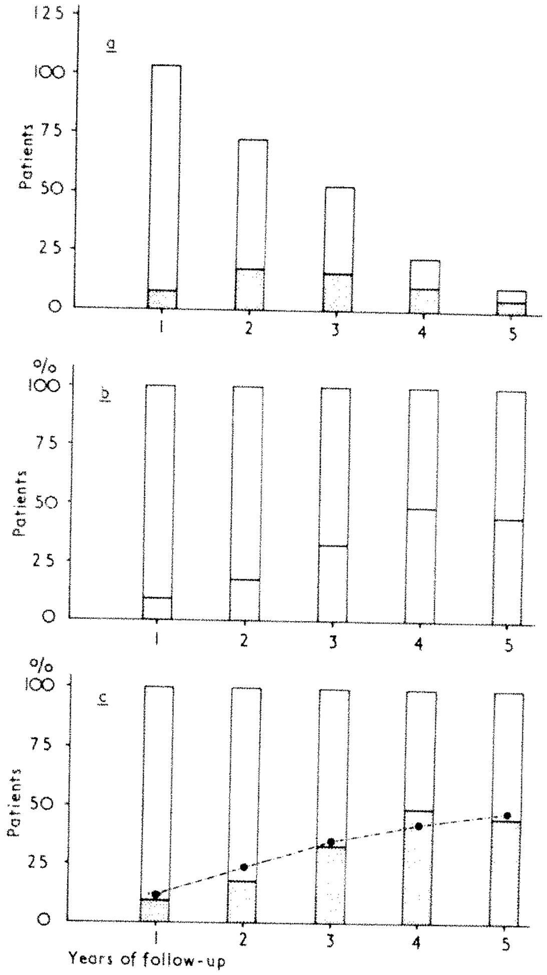


Fig. 1 *Patient results.* (a) *Proportion of patients who developed a disciform lesion in the second eye over the period of follow-up (shaded section of column).* (b) *Same expressed as percentages.* (c) *Comparison with calculated incidence curve of 12% per year*

Comments

In respect of yearly incidence the risk of developing a disciform lesion in the second eye appears to lie between 12 and 15%. This is in agreement with the incidence of 12% found by Teeters and Bird (1973), and 35% in 3½ years by Gass (1973). The results in terms of patient follow-up suggest a constant risk of 12% per year of developing a second disciform lesion during the first 5 years. A second disciform lesion does not appear to be inevitable within any given period. It is unlikely that the risk in the 60 to 69 age group can be applied to younger patients. Equally the risk may not pertain to people with

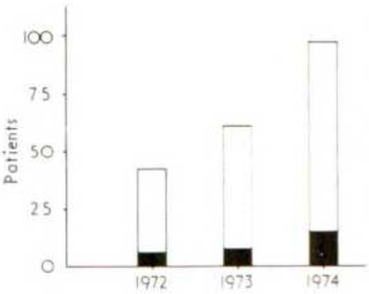
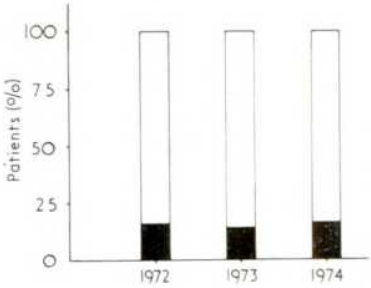


Fig. 2. *Yearly results.*

(a) *Proportion of patients who developed a disciform lesion in the other eye each year (shaded section of column).*



(b) *Same expressed as percentages*

bilateral drusen and pigment epithelial changes without disciform lesions.

Gass (1973) has clearly shown the relatively lower risk of developing a disciform lesion in these two groups. In his series a smaller proportion of eyes in patients with no disciform lesions suffered visual loss than in those with unilateral disciform degeneration, and in the latter group the average age of patients suffering visual loss in the second eye was higher than in the original sample.

II. SIGNIFICANCE OF PREDISCIFORM CHANGES IN THE SUBSEQUENT DEVELOPMENT OF SENILE DISCIFORM MACULAR DEGENERATION

Materials and methods

All 104 patients in the original sample had a full ophthalmological examination which included fundus colour stereophotography and fluorescein angiography. All the patients have had repeated examinations during the period of follow-up (29 of these 104 patients developed a disciform lesion in the other eye during this period).

A Zeiss (Oberkochen) fundus camera was used to obtain both colour photographs and fluorescein angiograms. The initial colour photographs and fluorescein angiograms of the eye with predisciform changes were examined under magnification. The macular region was arbitrarily divided into sectors by placing a grid over the photograph (Figs. 3 and 4). Both drusen and pigment epithelial changes were examined on the initial colour stereophotographs.

The following characteristics of drusen were assessed: Total number and distribution, whether macular or perimacular. Single dome-shaped drusen were arbitrarily divided into four categories according to their diameter: Less than 50 µm; 50 to 150 µm;

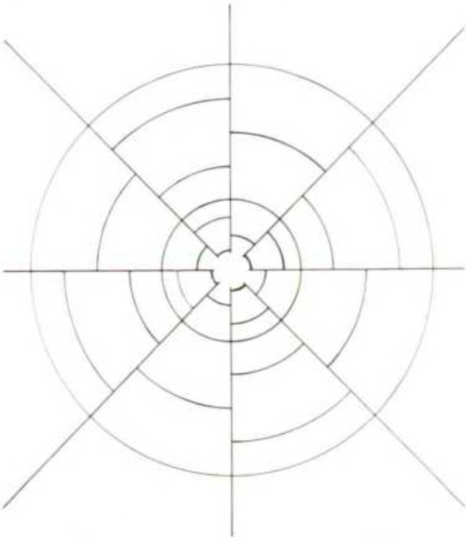


Fig. 3 *The measuring grid. Inner complete ring corresponds to a diameter of 1600 µm (1 DD), outer ring to 4800 µm (3 DD). The distances between the dividing marks correspond to 200 µm in the inner ring and 400 µm in the outer ring*

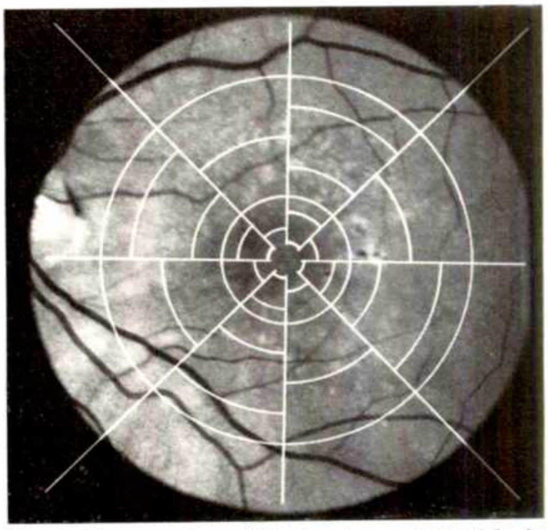


Fig. 4 *The measuring grid is placed on a standard fundus photograph, centred on the fovea. The size and distances of fundus abnormalities can be assessed*

200 to 500 μm; 500 to 800 μm. Sheets of white sub-pigment epithelial material with an irregular surface were categorised as confluent. In respect of the edge of the drusen, they were separately recorded as having well-defined or blurred edges.

The corresponding fluorescein angiograms were examined. The following features were noted: accumulation of dye, transmission defect or a normal appearance. All the findings were recorded on a standard form. Pigment epithelial changes were recognised either as pigment clumping on the surface of the drusen or without underlying drusen, and as pigment epithelial atrophy with or without co-existing choroidal atrophy.

Although the following features were recorded, they were not used in the final analysis. The colour of drusen was difficult to assess because of variation in the quality of the original photographs or lens opacities or the likelihood of observer error. Drusen with white glistening surfaces, usually thought to denote calcification, were observed infrequently. In the presence of widespread drusen pigment epithelial atrophy without choroidal atrophy was also difficult to estimate.

To minimise bias and to maintain standardisation, the following steps were adhered to: (1) The patient records were examined at random without prior knowledge of the examiner as to which patient subsequently developed a disciform lesion in that eye; (2) all findings were tape-recorded at first, so that no pattern could be observed from the record form before the investigation was completed; (3) repeatability tests were performed.

After completion of the study, patients who developed a disciform lesion in the second eye were identified (group I) and compared with those patients who remained at the predisciform stage (group II). The results were analysed with the aid of a computer, using the χ^2 method.

Results

I. DRUSEN

Drusen were found in all the patients studied.

Number and distribution

No significant difference in number of drusen was found between the two groups. This was so both in the macular and perimacular areas.

Size

Small drusen (less than 50 μm) were found more commonly and large drusen (500 to 800 μm) less so in eyes which remained free of disciform lesions (group II) than those which developed a disciform lesion (group I), though at a low level of significance ($P = 0{\cdot}0207$ and 0·0844 respectively).

Patients who subsequently developed disciform degeneration (group I) had more areas of confluent drusen than patients in group II. The difference is highly significant ($P < 0{\cdot}001$). All of the 13 patients with confluent drusen in the second eye followed up for more than 2 years developed a disciform lesion in this eye. The incidence of second eye involvement was 5 of 9 followed for 2 years and 3 of 16 followed for 1 year.

Demarcation from surrounding retina

No significant difference in prognosis was found between drusen with well-defined or blurred edges.

II. FLUORESCEIN ANGIOGRAPHIC APPEARANCE

Accumulation of dye in the late venous phase was observed more frequently in patients who subsequently developed disciform degeneration. The difference between the two groups is highly significant ($P = 0{\cdot}001$). The incidence of second eye involvement in those patients with dye accumulation was 18 of 27 in those patients followed for over two years, 6 of 14 followed up for 2 years, and 3 of 18 followed for 1 year. Conversely, drusen which gave rise to no change in the background choroidal fluorescence were found more commonly in group II than in group I ($P = 0{\cdot}0022$). There was no significant difference between the two groups with regard to transmission defect.

III. PIGMENT EPITHELIAL CHANGES

No significant difference between the two groups was found for pigment clumping on the surface of drusen or unassociated with drusen.

Subsequent development of disciform degeneration

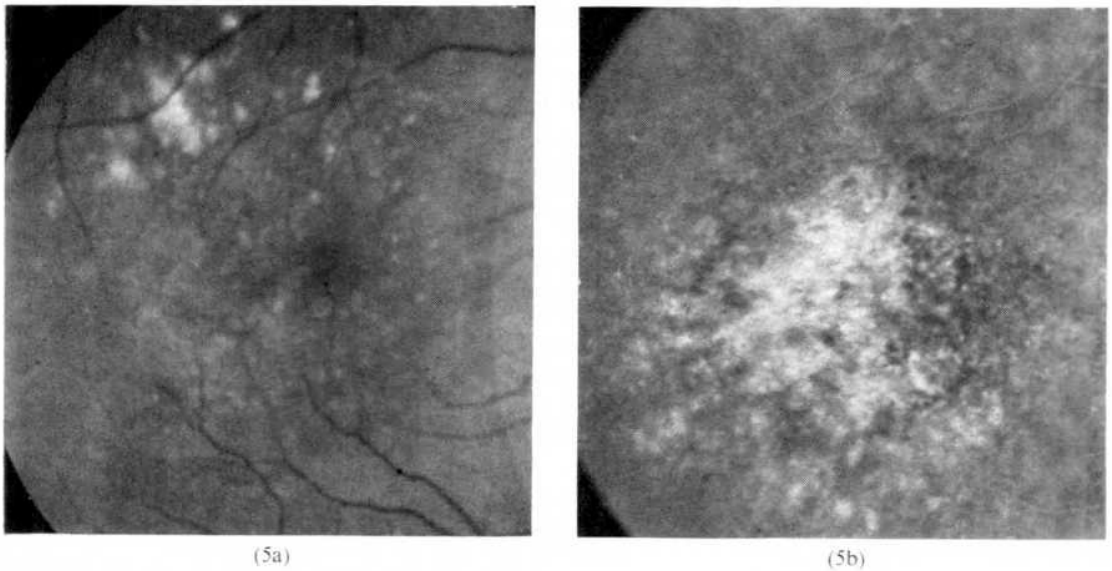
Of the 29 patients who subsequently developed a disciform lesion in the second eye the origin of the subretinal neovascular tissue could be related to pre-existing lesions in 25.

In 20 patients the neovascular tissue arose at the site of drusen with accumulation of dye (Figs. 5 and 6). In 5 patients neovascularisation occurred in areas which originally showed mainly transmission defects as well as some accumulation of dye (Fig. 7).

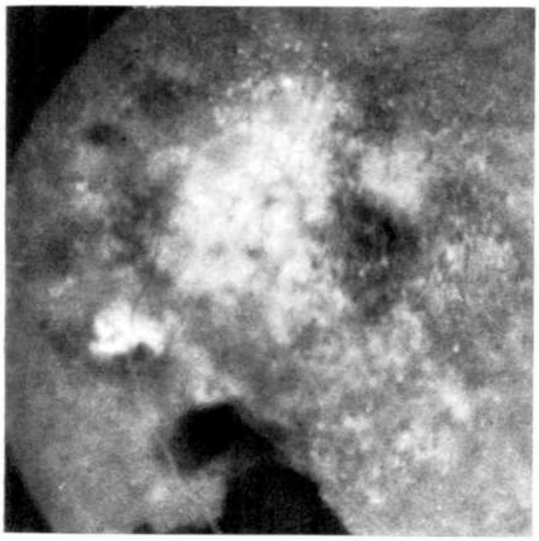
One patient developed a disciform lesion in an area which appeared normal on the original angiogram. The origin of the neovascular tissue could not be identified in the remaining 3 patients; in 2 the neovascularisation involved the entire macular and paramacular areas, and in 1 the relevant fluorescein study was not available.

Comments

These results suggest that patients with unilateral disciform lesions are at high risk of developing a



(5a) (5b)



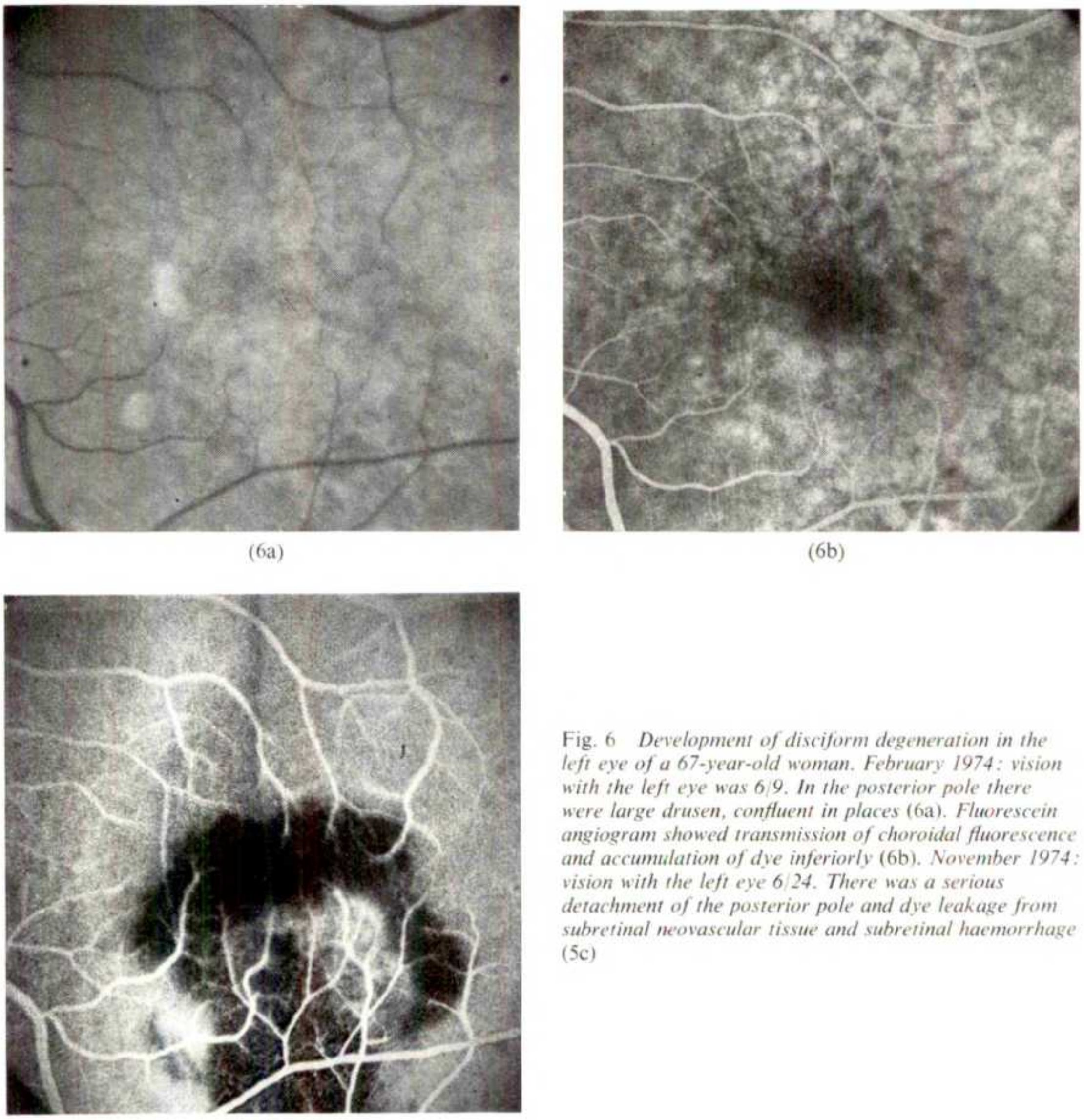
(5c)

Fig. 5 *Development of disciform degeneration in the right eye of a 68-year-old woman. August 1974: vision with the right eye 6/12 and in the posterior pole there were multiple confluent drusen* (5a). *Fluorescein angiogram showed intense hyperfluorescence corresponding to temporal drusen* (5b). *February 1975: vision with the right eye 6/36 with serous detachment of the posterior pole, subretinal haemorrhage and dye leakage from subretinal neovascular tissue in an area corresponding with the dye accumulation* (5c)

lesion in the second eye if there are large confluent drusen in which there is progressive leakage of dye on fluorescein fundus angiography. Conversely, if drusen are small and do not alter the pattern of the background choroidal fluorescence, the risk of visual loss in the second eye is relatively less.

It is likely that the large areas of subpigment epithelial white deposits which we have termed confluent drusen are similar to the basal linear deposits described by Sarks (1976). The significance of accumulating fluorescence within drusen is uncertain. It is acknowledged that penetration of Bruch's membrane by choroidal blood vessels occurs more commonly than is clinically evident, particularly in areas of accumulation of abnormal material on the inner surface of Bruch's membrane (Sarks, 1976). Blood vessels within drusen would certainly account for dye accumulation during angiography, and it is thus not surprising that this clinical finding should indicate a poorer visual prognosis.

These findings are important in defining the risk of disciform degeneration in a second eye, and also in the design of clinical trials to determine whether photocoagulation alters the incidence of disciform


(6a)

(6b)

(6c)

Fig. 6 *Development of disciform degeneration in the left eye of a 67-year-old woman. February 1974: vision with the left eye was 6/9. In the posterior pole there were large drusen, confluent in places* (6a). *Fluorescein angiogram showed transmission of choroidal fluorescence and accumulation of dye inferiorly* (6b). *November 1974: vision with the left eye 6/24. There was a serious detachment of the posterior pole and dye leakage from subretinal neovascular tissue and subretinal haemorrhage* (5c)

degeneration developing in an eye with drusen. Having identified high- and low-risk factors, these characteristics should be recorded, and ideally the patients stratified in respect of these factors before they are randomised.

We should like to thank Mr K. S. Sehmi for his photographic expertise and Miss J. Fisher for her secretarial assistance. We are particularly grateful to Mr H. Donovan, who undertook the statistical analysis.

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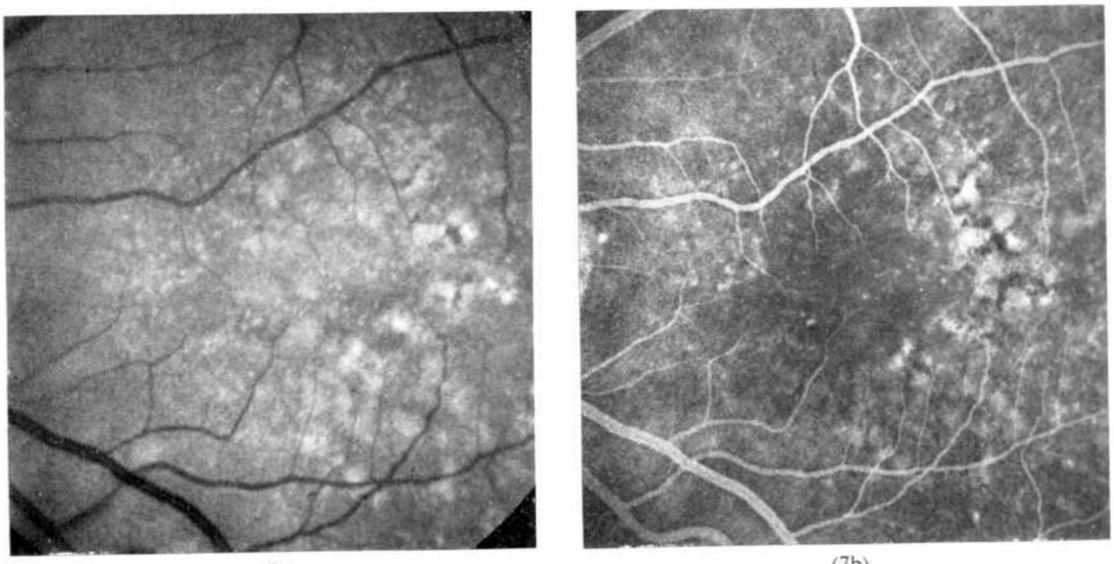
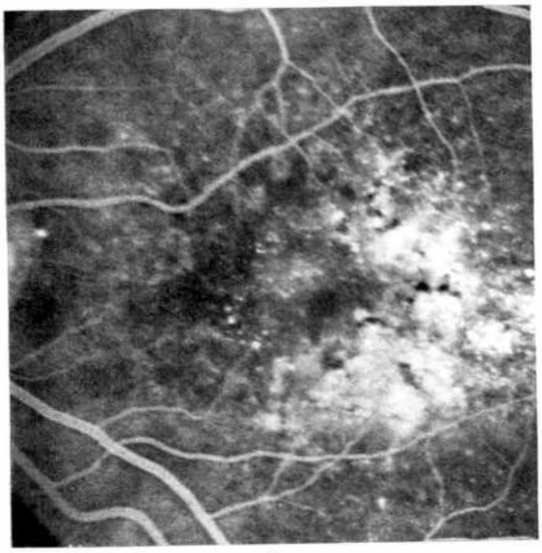


(7a) (7b)



(7c)

Fig. 7 *Development of disciform degeneration in the left eye of a 62-year-old woman. May 1971: vision in the left eye was 6/6 and in the posterior pole there were confluent drusen* (7a). *Fluorescein angiogram showed transmission of choroidal fluorescence as well as accumulation of dye* (7b). *July 1972: vision with the left eye 6/36 with serous detachment of the posterior pole and dye leakage from subretinal neovascular tissue* (7c)

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Response of the human eye to laser irradiation of the iris

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SUMMARY Irradiation of the iris of glaucoma patients with either a ruby or an argon laser caused no obvious disruption of the blood-aqueous barrier (as visualised by fluorescein angiography), in contrast to a sudden and pronounced effect in the rabbit eye. Only a low and variable increase in intraocular pressure occurred in the human subjects after the laser irradiation in comparison with a consistently high rise of ocular tension in the rabbit. This investigation indicates that the human eye is much less responsive to injury.

Since the rabbit is the experimental animal most frequently used in investigative ophthalmology, it is important to establish the extent to which the acute inflammatory response of the rabbit eye to noxious stimulation is representative of that in man. There are notable anatomical differences between the structure of the anterior uvea in primates and rabbits which most probably account for the significant differences in the pattern of changes and the sensitivity of the respective eyes to trauma (Prince, 1964; Hogan *et al.*, 1971). Anterior chamber paracentesis, for example, in the monkey causes only a slight infiltration of a blood plasma protein marker, which appears to enter the chamber by a retrograde passage through the outflow channels (Raviola, 1975), whereas in the rabbit eye a sudden and pronounced influx of protein occurs primarily across the ciliary processes (Unger *et al.*, 1975).

Ruby laser irradiation of the rabbit iris, like mechanical or chemical irritation, provokes a rapid ocular response consisting of immediate vasodilatation of the anterior uveal vessels, constriction of the pupil, and an increase in the intraocular pressure (IOP). Perhaps the most striking and least easily prevented change in the rabbit is a sudden breakdown of the blood-aqueous barrier (Larsson, 1930; Duke-Elder and Duke-Elder, 1931; Davson and Huber, 1950; Sears, 1960; Ambache *et al.*, 1965; Fontenberry *et al.*, 1969; Bethal and Eakins, 1972; Cole and Unger, 1973; Unger *et al.*, 1974).

The clinical use of the laser in treating glaucoma due to angle closure afforded a unique opportunity to study the reaction of the human eye to a moderate form of trauma. In the following report fluorescein angiography of the iris performed shortly after the application of the argon or the ruby laser to the iris of such patients demonstrated the relative stability of the blood-aqueous barrier in the human eye after laser irradiation of sufficient energy to elicit a decided effect in the rabbit.

Materials and methods

Patients selected for the present study had glaucoma for which laser treatment was clinically indicated (Perkins and Brown, 1974). Most of the subjects were being treated with one or more of the following drugs: 1 to 4% pilocarpine, 0·5% eserine, 0·1 or 1% neutral adrenaline, acetazolamide 250 mg tablets, or 0·3% prednisolone (see Table 1). Generally, the last administration of any drug occurred 3 to 4 hours before laser irradiation.

LASER TREATMENT

Since exposure of a pigmented iris to the argon laser destroys stromal tissue and induces melanocyte infiltration into the site of the lesion, argon laser irradiation is routinely used to effect shrinkage of the anterior surface of the iris proximal to the angle and to prepare a target-site of deep pigmentation for subsequent ruby laser irradiation. Consequently, the ruby and/or the argon laser may have been used on several occasions to treat the same iris in an effort to achieve a full thickness iridotomy. Many of the patients, therefore, had received previous laser treatment (see Table 1).

Ruby laser irradiation. A single emission of the ruby laser consists of a 0·6 ms pulse train, having an integrated energy of 550 to 650 mJ, which was focused on an area of iris of about 1 mm diameter

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Table 1 *Fluorescein photography of the anterior segment following irradiation of the iris in patient volunteers*

Subject		*Diagnosis*[1]	*Previous*[2]		*Laser dose*[3]			*Medication*[4]	*IOP rise*[6]	*Fluores.*[5]	*Differences*[7]
Age	*Sex*		*Argon*	*Ruby*	*µm*	*mW*	*X*		*mmHg*	*Leakage*	
(*Argon laser irradiation*)											
50	Male	CAG	—	—	200	100	81	2% P	15	0·5	0·5
69	Female	CAG, small synechiae	1 (90)	—	200	250	90	4% P 0·1% A	2	1·0	ND
66	Female	CAG, diabetic, rubeosis?	1 (31)	—	100	500	22	4% P 250D	1	0·5	0·5
64	Female	SG, bombe iris	—	—	50	500	28	0·3% Pred 250D	8	<0·5	ND
73	Male	CAG, iridectomy fellow eye	—	—	100	200	32	4% P 1% A	20	0·5	less
60	Female	CAG	—	—	100	300	63	0·25% E	5	<0·5	ND
(*Ruby laser irradiation*)					(*mJ*	*X*)					
71	Female	CAG	2 (78)	1 (1)	550	2		1% P 0·3% Pred	14	<0·5	ND
76	Female	CAG	2 (184)	—	550	2		2% P 0·3% Pred	2	<0·5	ND
60	Male	CSG	1 (3)	1 (3)	550	2		—	6	<0·5	less
51	Female	CAG	1 (26)	—	650	2		2% P	7	<0 5	less
66	Female	CAG, diabetic, rubeosis?	2 (127)	—	650	3		4% P 250D	5	0·5	0·5
60	Male	CAG	—	—	650	3		2% P	3	<0·5	ND

[1] CAG—closed-angle glaucoma; SG—secondary glaucoma; CSG—chronic simple glaucoma.
[2] Number of laser sessions (total number of applications).
[3] For the argon: µm—micron spot size diameter; mW—milliwatts; X—number of applications.
For the ruby: mJ—millijoules; X—number of applications.
[4] P—pilocarpine; A—neutral adrenaline; D—Diamox (acetazolamide); Pred—prednisolone; E—eserine.
[5] Fluorescence of aqueous humour scored from 0 (nil) to 10 (completely filled; *cf.* Unger *et al.*, 1975). IOP—intraocular pressure.
[6] Rise of IOP at 40 min after laser irradiation.
[7] Difference in leakage between irradiated and fellow eye at 15 min after injection.

using a modified slit-lamp apparatus described by Perkins and Brown (1973). In the present study the laser was usually applied 2 or 3 times to the iris of each subject.

Argon laser irradiation. Argon laser light was generated by a Coherent 800 Argon-Laser Photocoagulator (Coherent Radiation; Palo Alto, California), which emits a continuous beam of variable diameter and intensity. Treatment consisted of multiple applications (up to 150) of a laser beam, usually of 50, 100, or 200 µm diameter, each for a duration of about 0·2 s with an energy of 100 to 1000 mW (specific conditions have been summarised in Table 1).

Fluorescein angiography. To demonstrate any breakdown in the blood-aqueous barrier a 20% solution of sodium fluorescein (0·1 ml/kg body weight) was injected rapidly into the brachial vein 10 to 15 minutes after treatment with the laser. Photographs of the anterior segment were taken at desired intervals over a 15-minute period using a 35-mm motorised Nikon camera. Illumination was provided by xenon flash tube and an arrangement of appropriate filters to ensure that only the fluorescence of the dye was recorded. The procedure has been described more fully by Cole (1974), Unger *et al.* (1974), and Edwards (1975).

IOP changes after laser irradiation. The IOP was measured by applanation tonometry before and at intervals over a 75-minute period after irradiation. The response was usually maximal at 40 minutes. Subjects included only those in whom the last administration of pilocarpine (and, in a few cases, acetazolamide or adrenaline with pilocarpine) had been not less than 3 hours prior to laser application.

Laser irradiation of the rabbit iris. To simulate conditions encountered in the patients Dutch rabbits were pretreated with either topically applied pilocarpine and eserine or neutral adrenaline and/or intramuscularly or intravenously injected acetazolamide (see Table 2). Animals weighing 2 to 2·5 kg

Table 2 *Response of the rabbit eye to laser irradiation of the iris*

Type	*No.*	*Medication*[1]	*Laser dose*[2]			*IOP rise*[3]		*Fluorescein*[4] *leakage*
						10 min	*30 min*	
(*Ruby laser irradiation*)			(mJ	X)				
Dutch	1	1	550	2		30	28	5
	1	1	550	3		25	20	7
	1	2	550	2		24	22	6
	1	3	550	2		25	20	6
	1	4	550	2		28	26	7
	1	5	550	2		26	22	5
	1	—	550	1		—	—	5
	1	—	550	2		25	20	6
	1	—	650	2		—	—	6
	3	—	550	3		—	—	6–8
	10	—	550	4		31+1	28+1	
New Zealand	1	—	550	2		—	—	—
	1	—	550	6		—	—	—
(*Argon laser irradiation*)								
			(µm	mW	X)			
Dutch	16	—	500	750	5	—	—	—
	4	—	500	750	5	—	—	4–7
New Zealand	2	—	500	750	5	—	—	—
	2	—	500	750	5	—	—	—

[1] Numbers refer to drugs outlined in the text.
[2] mJ—millijoules; µm—spot size in microns; mW—milliwatts.
X—number of applications of the laser.
[3] IOP increase in mmHg at 10 and 30 min after irradiation.
[4] Fluorescence of the anterior chamber at 10 min after injection scored according to an arbitrary scale from 0 (nil) to 10.

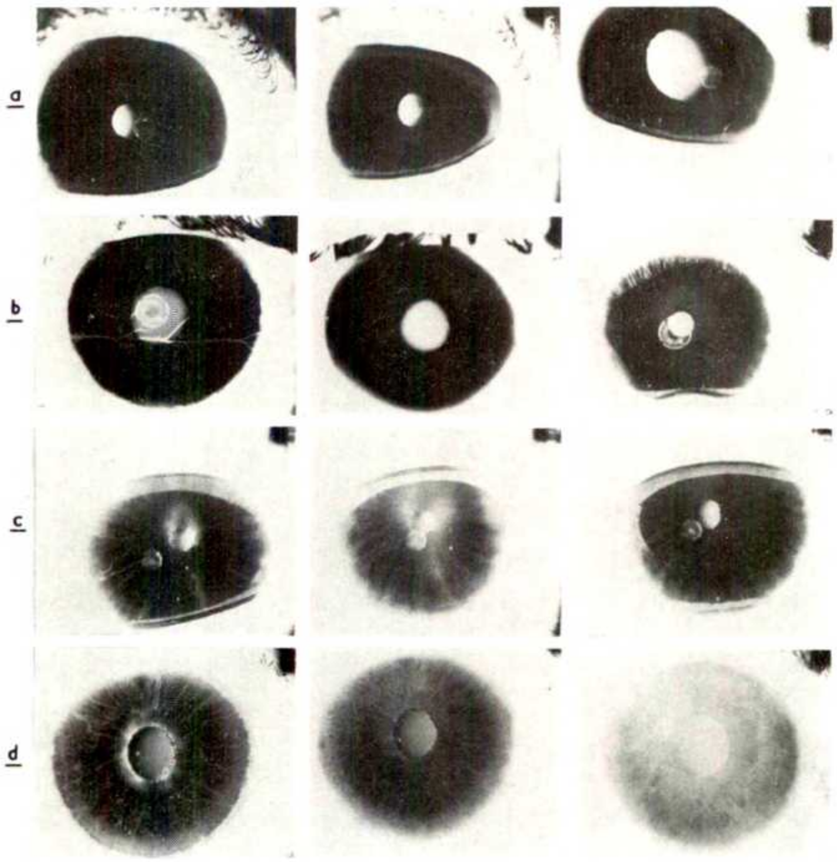

Fig. 1 *Fluorescein angiography of the anterior segment of the human eye following laser irradiation of the iris. The appearance of fluorescein is shown at 2 and 10 min in the irradiated eye and at 10 min in the untreated contralateral eye (from left to right) in* (a) *a 76-year-old female after 2 ruby laser applications;* (b) *a 60-year-old female after 63 argon laser applications;* (c) *a 66-year-old female after 3 ruby laser applications; and* (d) *a 60-year-old male after 2 ruby laser applications*

were placed in a holding tray and anaesthetised by an initial intravenous injection of 30 mg/kg sodium pentobarbitone. Ten to 15 minutes after irradiation a fluorescein angiogram was carried out. In other experiments the IOP was determined by applanation tonometry before and at desired times up to 60 minutes after application of the argon or ruby laser.

Results

Fluorescein angiography after ruby laser irradiation in humans. A fluorescein angiography was carried out in 6 subjects 10 to 15 minutes after irradiation at 2 to 3 sites on the upper half of the iris. All but 1 subject had had prior argon and 2 had prior ruby laser treatment. Only 1 patient had had no previous medication (summarised in Table 1).

Virtually no influx of fluorescein into the anterior chamber was visible over the 15-minute period of photography in either the test or the contralateral eye in 5 subjects (see Fig. 1*a*). Some fluorescence was apparent over the pupil, but this was due to the natural fluorescence of the lens itself.

In one diabetic subject a local fluorescence was seen at the pupil margin (from permeable, possibly rubeotic vascular loops) (see Fig. 1*c*). Another subject exhibited a similar leakage, but by 10 minutes after injection the fluorescence was greater in the contralateral eye (see Fig. 1*d*).

Fluorescein angiography after argon laser irradiation. Six patients, 2 of whom had had previous argon laser treatment, were irradiated according to schedules summarised in Table 1. In 4 of them no noticeable difference was seen between the treated and the fellow eye in the extent of fluorescein infiltration into the anterior chamber (see Fig. 1*b*). A moderate but diffuse fluorescence appeared in the anterior chambers of both eyes of a fifth patient, apparently coming from the anterior surface of the irides (see Fig. 2*a*). The contralateral eye of a sixth patient, which had experienced a surgical iridectomy 17 years earlier, exhibited some fluorescein leakage exceeding that seen in the irradiated eye (see Fig. 2*b*). In 2 patients, 1 with a possible rubeosis, a slight vascular leakage near the pupil margin of the irradiated iris was evident (see Figs. 3*a* and *b*).

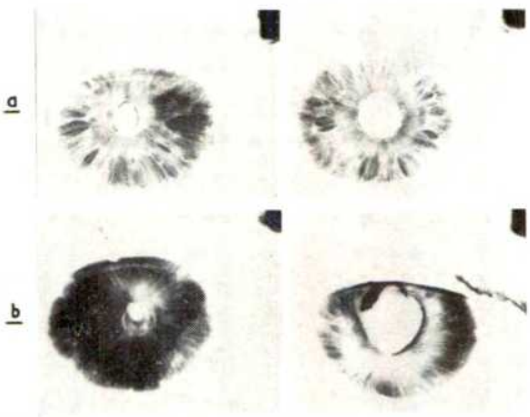

Fig. 2 *Fluorescein angiography following argon laser irradiation. The appearance of the fluorescein is seen at 10 min after injection in the irradiated (left) and fellow eye (right) in* (a) *a 69-year-old female given 90 applications and* (b) *a 73-year-old male receiving 32 applications and presenting a contralateral eye with a surgical iridectomy*

Breakdown of the blood-aqueous barrier in the rabbit following laser irradiation. By contrast with the human subjects, an obvious and pronounced laser-induced disruption of the blood-aqueous barrier was demonstrated in the rabbit using the fluorescein procedure. The extent of fluorescein infiltration into the aqueous humour of an eye receiving 1 to 3 laser lesions was considerably greater at 10 to 15 minutes after injection than in man (scored 4 to 9 compared to 0·5 or less in man on an arbitrary scale from 0 to 10, *c.f.*, Unger *et al.*, 1975; see Table 2 and Fig. 4). It was obvious in the rabbit that the bulk of the fluorescein entered the anterior chamber via the pupil and was apparently associated with a plasmoid aqueous of greater density than normal aqueous since it settled by gravity into the lower half of the chamber.

A similar effect was observed in 4 rabbits receiving argon laser irradiation (200 or 500 µm, 750 mW, 5 times at 0·5 s each application; see Fig. 4*d*). It was of some interest that neither ruby nor argon laser irradiation of the non-pigmented rabbit iris (New Zealand variety) produced a breakdown of the blood-aqueous barrier (see Table 2 and Figs. 4*e* and *f*).

In order to compare more closely the results found in patients with that of the rabbit, rabbits were treated with the following drugs over a given period immediately before irradiation at a single site on the iris: (1) 2% pilocarpine and 0·5% eserine administered topically as 1 drop/5 min over 60 minutes; (2) 2 drops of 0·1% neutral adrenaline 60 minutes previously; (3) 25 mg/kg acetazolamide injected intramuscularly 4 hours previously; (4) 25 mg/kg acetazolamide injected intravenously 15 minutes prior; and (5) a combination of that given in (1) and (4). In every case a sudden influx of fluorescein was visualised (a score of 4 to 7; see Table 2 and Fig. 4*c*) on angiography.

Comparison of the IOP rise following laser irradiation in man and the rabbit. In the 12 additional patients, the IOP was followed up to 75 minutes after irradiation. A slow rise in pressure with a broad peak between 40 and 60 minutes occurred in all patients, but the maximum rise only exceeded 10 mmHg in 3. The height of the response did not seem to be related to the type of laser, the energy level, or previous medication.

Data on the response of the IOP to laser treatment was available for an additional 27 patients and also showed a variable rise in pressure from 0 to 24 mmHg

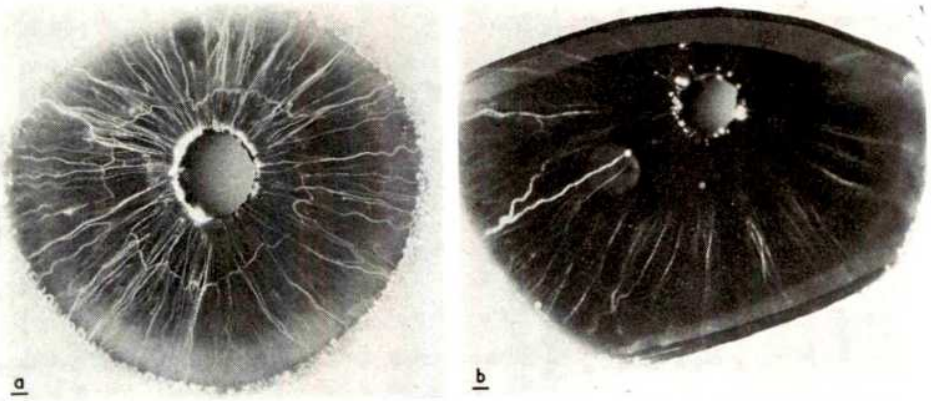

Fig. 3 *Fluorescein angiography following ruby laser irradiation. Fluorescein is seen to leak from permeable iris vessels near the pupil margin* (a) *30 s after dye injection in a 60-year-old male receiving 3 laser applications and* (b) *at 18 s in a 66-year-old female having 3 laser applications*

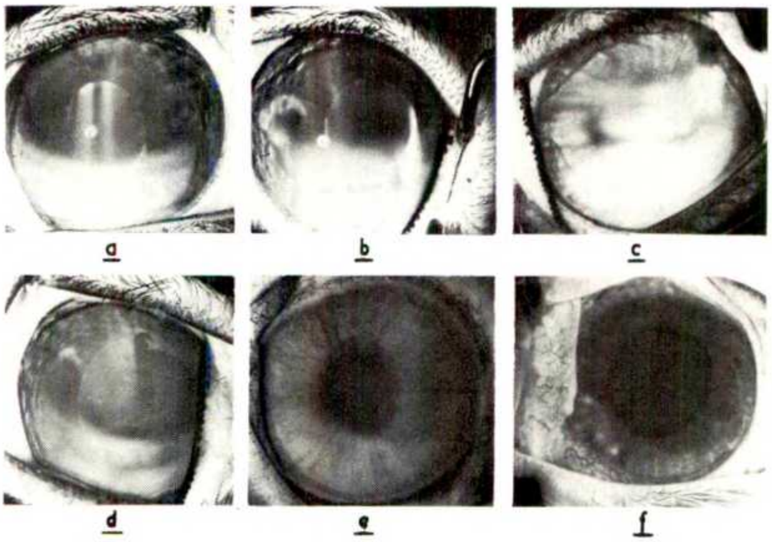

Fig. 4 *The sudden breakdown of the blood-aqueous barrier is indicated by the influx of intravenously injected fluorescein following laser irradiation of the pigmented rabbit iris with* (a) *1 and* (b) *2 ruby laser applications and* (c) *2 applications in an eye pretreated with pilocarpine, but not* (f) *in an albino rabbit eye receiving 6 applications. A similar appearance of fluorescein occurred* (d) *in the pigmented eye but not* (e) *the albino eye receiving 5 applications of argon laser light (0·5 s; 500 μm). All photographs were taken 10 min after injection of fluorescein*

after ruby laser treatment and 0 to 20 mmHg after argon laser irradiation. Again there was no obvious correlation between the rise in IOP and the number of applications, the energy level, or the medication.

By contrast, the response in the rabbit to either laser reached a peak at about 15 to 20 minutes and declined to 50% at about 40 minutes (argon) and 50 minutes (ruby) after irradiation (see Fig. 5). The peak IOP rise after ruby laser irradiation (4 applications; 550 to 600 mJ) was 31 mmHg (± SE 1; 10 experiments) and after argon irradiation (5 applications of 500 μm, 750 mW, 0·5 s) was 18 mmHg (± SE 2; 14 experiments). Administration of drugs comparable to that used in the patients had essentially no effect on the IOP change (see Table 2).

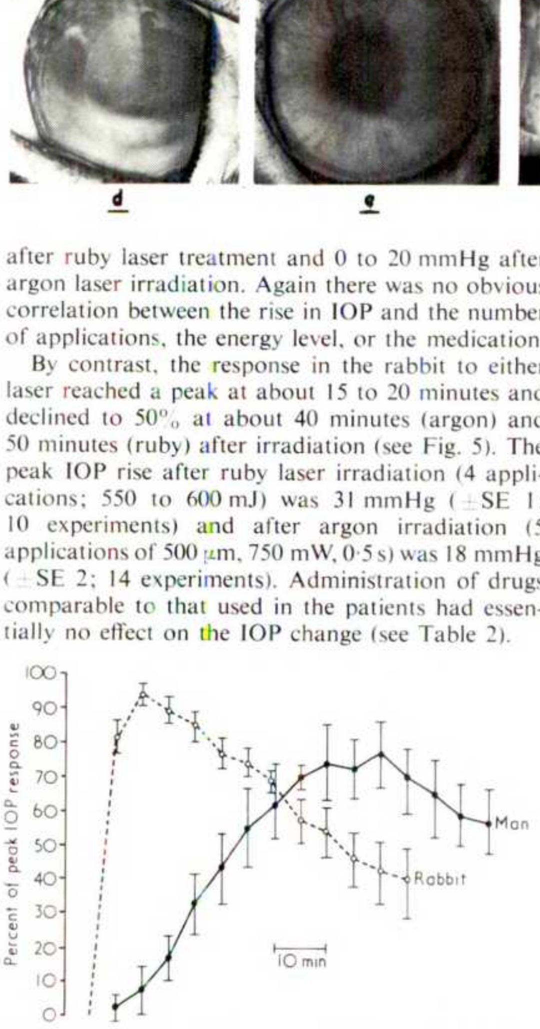

Fig. 5 *Percentage of the maximal IOP rise following laser irradiation plotted against time. The curve for man includes only those exhibiting a peak response greater than 5 mmHg. The results obtained with both the argon and the ruby laser have been pooled. Each point shows the mean ± SE*

Discussion

Stimulation of the human iris with ruby or argon laser light caused very little obvious disturbance of the blood-aqueous barrier as assessed by fluorescein angiography. Unlike the rabbit eye, which suffers an immediate and marked breakdown, the extent of fluorescein infiltration into the anterior chamber was about the same in the treated as in the contralateral (control) eye. In several subjects some diffuse fluorescein was seen to enter the anterior chamber apparently from the anterior surface of the iris, in two cases near the pupil margin. In the rabbit, however, fluorescein entered via the pupil, associated with dense, presumably plasmoid, secondary aqueous after ruby or argon laser irradiation (see Unger and Bass, 1977). Thus in man what dye does enter the anterior chamber probably arrives from dilated iridial vessels, whereas in the rabbit there is an overt breach in the blood-aqueous barrier of the ciliary processes, ostensibly by a bulk flow of extravascular fluid across the ciliary epithelium (see Cole, 1974; Unger *et al.*, 1974, 1975). It is unlikely that the observed difference between man and the rabbit is due to the previous medication or to the clinical status of the patients. Instead, the greater sensitivity of the rabbit eye to trauma and the instability of the blood-aqueous barrier reflect gross anatomical differences.

The ciliary bodies of the rabbit eye have long iridial processes (as well as a more posterior group) extending radially along the posterior surface of the iris; in places the two structures share the same epithelial covering, and thus the stroma of the iris and ciliary processes are continuous (Prince, 1964;

Kozart, 1968). Thus injury to the rabbit iris and any concurrent release of a chemical mediator would be readily transmitted through the stroma to the ciliary processes. Indeed, after anterior chamber paracentesis, ruby laser irradiation of the iris, or intracameral instillation of various vasodilator drugs the blood vessels in the tips of the ciliary processes (but not the iris) are seen to take up intravenously injected colloidal carbon, an indication of increased permeability (Unger *et al.*, 1974; Cole, 1975). Consequently, oedema develops in the rabbit iridial processes followed by a breakdown in the blood-aqueous barrier of the ciliary epithelium (Kozart, 1968). In man by contrast the ciliary processes are more regular and are separated from the iris, so that they are less likely to be affected by the release of a chemical mediator from the iris.

A rapid and consistent elevation in IOP is a feature of the ocular response in the rabbit and is most likely to be due to vasodilatation as well as mechanical and osmotic effects caused by disruption of the blood-aqueous barrier. The rabbit response is mediated partly by E-type prostaglandin and by an apparent non-cholinergic neurogenic component (Neufeld *et al.*, 1973; Unger *et al.*, 1974, 1976). Although neither prostaglandin nor noxious stimuli appear to increase aqueous humour secretion (sodium transport), prostaglandin, at least, may stimulate fluid conductivity and solute permeability across (isolated) ciliary epithelia (Duke-Elder and Gloster, 1968; Green, 1974; Pederson and Green, 1975).

In man, the laser-induced IOP response seems less immediate, less intense, and very inconsistent from one individual to another; in over half of the subjects the IOP rise was less than 5 mmHg. Although the number of cases was limited, there was no apparent correlation between the rise in tension and age of the patient, the type of laser, or the number of laser applications. If an increase in aqueous formation (ultrafiltration) occurs in man after laser stimulation, then individual differences in outflow facility might possibly explain the wide variations as well as the delayed onset of IOP changes. Although an age-related increase in drainage resistance is uncertain, the tendency for an increase in the magnitude of variation between individuals seems greater in the elderly (Duke-Elder and Gloster, 1968) and the subjects in the present study were all over 50 years of age (64±SE 3). The therapeutic use of prednisolone might be expected to increase outflow resistance (Linnér, 1959; Armaly, 1963, 1964) whereas miotic agents would decrease the resistance (Krill and Newell, 1964; Linnér, 1958). However, in the present study there was no correlation between the size of the IOP change and treatment with prednisolone, pilocarpine, or acetazolamide (which would decrease aqueous formation).

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Incidence and causes of blindness among the under 5 age group in Malawi

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SUMMARY The expected incidence of blindness among children under 5 years of age in Malawi is 34 cases per 100 000 children. Direct ocular infections were responsible for the blindness in 32% of the cases (bacterial infections 20% and measles 12%). The instillation of traditional medicine in these cases worsened the ocular condition and induced in all of the cases a 'hopeless' situation of total melting of the cornea and protrusion of the uvea. Congenital factors (excluding retinoblastomas) were responsible for 30·8% of the blind cases. Among these, 11 cases of congenital cataracts were successfully treated and will not appear as blind in future. A high incidence (9·3%) of cortical blindness was recorded. Trauma was implicated in 5·3%, while retinoblastoma was found in 8%.

It is believed that adequate preventive measures should be able to lower the incidence of blindness among this age group to 5 cases instead of 34 per 100 000 children.

In a previous paper (Chirambo and BenEzra, 1976) we reported a retrospective study of the causes of blindness among 270 blind students attending 17 blind school institutions in Malawi. It was found that infections as a group were the main cause of blindness, while measles was the most common single cause. At the period when most of these students became blind the prevalence of blindness in Malawi (then Nyasaland) was estimated at 300 to 500 (or more) cases per 100 000 inhabitants. These numbers corrected to give the incidence among children are believed to be even higher (Phillips, 1961; Merin, 1967). These data were based mostly on the 'impression' of the ophthalmologist or on a very small pilot study excluding adequate representation of the group of children under 5 years of age, a group with the highest incidence of blindness in developing countries. From our experience, we estimated the incidence of blindness in this age group in the early 1960s at 400 (or more) blind per 100 000 children. The relative contribution of this age group to the evaluation of the prevalence of blindness could not be adequately reflected, as the mortality rate among blind young infants in developing countries was very high. Following 10 years of sponsorship of ophthalmological care in Malawi by the department of ophthalmology of the Hadassah Hebrew University of Jerusalem, Israel, a study of the causes and incidence of blindness among the population of children under 5 years of age was undertaken. Adequate statistical evaluation of the population of children in the different districts was available as the consequence of an extensive campaign for the promotion of maternal and child health on a national basis (Malawi Ministry of Health, 1975). To the best of our knowledge this is the first study of the causes and incidence of blindness among the whole child population under 5 in an African country.

Methods

Malawi is divided into 24 districts. Each district has a district hospital and peripheral dispensaries, the number of which varies according to the density of the population. The dispensaries are run by medical assistants, while the district hospital is in general directed by a medical officer (general practitioner) with the assistance of a clinical officer, medical assistants and nurses. All problematical cases needing specific care are referred to the central hospital in Blantyre. 11 ophthalmic medical assistants (non-graduate) are posted in the most densely populated districts. They deal with routine cases and minor surgery, while all ocular problems and major surgery are referred to the eye department

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in Queen Elizabeth Central Hospital in Blantyre directed by two eye specialists. This system, although not perfect, enables most of the ophthalmic cases to be seen by an ophthalmic medical assistant while problematical cases are referred to the ophthalmologist. Patients selected to be seen by the eye specialist are provided with travel warrants from their home to the central hospital.

It is estimated that some 25% of all cases needing eye care are seeking traditional treatment (local medicine) or are treated in missionary institutions all over the country. Most of these are also referred to us, especially when the outcome is blindness.

The number of children under 5 years of age among the Malawi population has been estimated at nearly one million (947 900) (Malawi Ministry of Health, 1975).

From 1 June 1975 to 31 November 1975 we have tried to collect all blind cases occurring among the under 5 age group all over the country. To promote accuracy we made frequent trips to the different districts during this period. However, it was quite impossible to visit each and every peripheral dispensary often enough. We feel that a 'true' incidence of blindness has been obtained in only 4 districts of the southern region. These had a population of 205 800 children under 5 years of age and were frequently visited by an ophthalmologist.

The criterion for blindness was arbitrarily scored when vision in the better eye was less than perception of familiar domestic objects at a distance of 1 m.

Results

The mean incidence during the studied period was 12·5 cases per month. The highest number of cases were seen during November (Table 1). 39 cases were boys and 36 were girls, a total of 75 cases in 6 months. Correction of these figures according to the incidence obtained from 4 districts of the Southern Region (Mangochi, Zomba, Chiradzulu, and Blantyre), where nearly every new blind case in this age group was seen and referred, gives a 'true' incidence of more than double the above. From these 4 districts, with a total population of 205 800 children under 5, a yearly incidence of 70 blind children is calculated (Table 2). This incidence can also be expressed as 34 cases per 100 000 children.

Table 1 *Monthly incidence of blindness during the period of study*

	June	*July*	*August*	*Sept.*	*Oct.*	*Nov.*	*Total*
Male	6	6	6	7	6	8	39
Female	6	5	8	4	5	8	36
Total	12	11	14	11	11	16	75

Table 2 *Incidence of cases according to districts*

District	*Population of children under 5 years*	*Number of blind cases*
Chitipa	13,700	1
Rumphi	10,800	2
Mzimba	52,900	6
Karonga	17,900	—
Nkhata Bay	19,400	—
Total Northern Region	114,700	9
Kasungu	22,500	1
Nkhotakota	14,500	—
Ntchisi	15,400	—
Dowa	42,000	2
Salima	20,000	1
Lilongwe	125,100	4
Mchinji	19,800	—
Dedza	53,200	2
Ncheu	37,900	5
Total Central Region	350,400	15
Mangochi*	43,700	8
Kasupe	52,000	4
Zomba*	65,100	12
Chiradzulu*	32,700	6
Mwanza	9,700	—
Blantyre*	64,300	9
Thyolo	57,400	5
Mulanje	91,900	3
Chikwawa	36,500	4
Nsanje	23,800	—
Total Southern Region	484,800	51

*These districts were often visited by the ophthalmologists, and the incidence obtained is believed to be the nearest to the 'true incidence'.

Among the causes of blindness direct ocular infections were found in 32% of all cases. Bacterial agents were responsible for 20% of all cases, while sequelae of measles (including superimposed bacterial infections) were the cause of blindness in 12% of all cases (Table 3). If the sequelae of encephalitis were added, the total incidence of blindness due to infections amounted to 38·7%. All the cases of ocular infections leading to blindness were referred at a very advanced stage. In most of these cases traditional medicine had been applied. This superimposed chemical factor resulted in most cases in total melting of the cornea and prolapse of the uvea. Trauma was responsible for 5·3% of the blind cases and retinoblastoma for 8.0% (Table 3). Other than retinoblastomas, 23 blind cases (30·8%) were due to a congenital cause. Among these, 11 cases of congenital cataracts were successfully operated. The high incidence of 9.3% due to cortical blindness is ill understood. Most of these cases were referred to the paediatric ward with a history of fever and severe headaches of 1 to 2 months' duration followed by a sudden blindness. Giant hydrocephalus inducing optic atrophy was responsible for the blindness in 6 cases (Table 3).

Discussion

When the figures from all 24 districts are considered, it appears that in Malawi there is an annual incidence

Table 3 *Causes of blindness among the 75 cases*

Cause	*Sex*		*Number*	*Total*	*%*	
	Male	*Female*				
Infections[1]				24		32
Bacterial	7	8	15		20	
Measles	2	7	9		12	
Trauma[1,2]	3	1	4		5·3	
Congenital				23		30·8
(1) Cataract[3]	4	7	11		14·7	
(2) Glaucoma	3	2	5		6·7	
(3) Macular degeneration	—	1	1		1·3	
(4) Toxoplasmosis	2	—	2		2·7	
(5) Syphilis	1	1	2		2·7	
(6) Retrolental fibroplasia	1	1	2		2·7	
Retinoblastoma[4]	3	3	6		8·0	
Optic atrophy						
(1) Post encephalitis	4	1	5		6·7	
(2) Hydrocephalus	4	2	6		8·0	
Cortical blindness[5]	5	2	7		9·3	
Total	39	36	75		100·1	

[1] Most of these cases used local medicine and were referred at a late stage. In all cases we failed to retain useful vision.

[2] Only in 2 cases the bilateral involvement was due to trauma. In 2 others 1 eye was previously blind due to infection.

[3] These cases were operated and will not appear in future as 'blind'.

[4] Only 4 cases were blind due to bilateral retinoblastoma. One case had a blind eye due to trauma and the other with retinoblastoma. In another case the fellow eye was blind owing to infection.

[5] In these cases the cause of blindness could not be defined accurately as anterior and posterior segments appeared normal.

of 15 blind cases per 100 000 children under 5 years. This is obviously an underestimate as in many districts, especially those far from Blantyre, the registration probably did not reflect the real incidence. A figure of 34 blind cases per 100 000 was obtained from the 4 districts where referral and registration of cases were optimal. If 21·4% of these are excluded as the result of successful cataract or trabecular operation, a yearly incidence of 27 blind children per 100 000 children under 5 is to be recorded. This incidence is nearer to the 'true' incidence over the country. If previous estimates are considered accurate, the incidence of blindness among children in Malawi as shown by this study has dropped during the last 10 years by 80 to 90%. This progress could be achieved only by the provision of a high standard of ophthalmological care throughout the country along with education (Michaelson, 1972). However, compared to the incidence of 3·8 blind cases per 100 000 children under 5 as found in most developed countries (Great Britain, 1968 to 1969; National Eye Institute, 1971), an incidence of 27 cases per 100 000 children is still 7 times higher than it need be. We believe the main causes of the disparity are the still widely used instillation of traditional medicine for the treatment of ocular infections and the deferment of medical consultation until an advanced stage of the disease. During 1975 15 cases of severe ophthalmia neonatarum and 32 cases of severe keratoconjunctivitis in children under 5 were admitted to the department in Blantyre. None of these used traditional medicine. As a result of treatment vision was restored in all cases. On the other hand useful vision was not restored in any of the cases that were referred after the use of traditional medicine and all of them remained blind.

Thirty-two per cent of the blindness was due to a direct ocular infection. This is a relatively low figure as compared to the data from a retrospective study demonstrating the frequency of infection as a cause of blindness in 75·2% of the cases (Chirambo and BenEzra, 1976). The incidence of 32% of blindness in Malawi due to direct ocular infection, although much lower than in the early 1960s and lower than the incidence in other African countries (Awdry *et al.*, 1967; Olurin, 1970), is nevertheless much higher than the figures reported from more developed countries (Merin *et al.*, 1972; Baghdassarian and Tabbara, 1975). This comparison indicates how much remains to be done in the prevention of blindness among children in Malawi.

An extensive campaign of education through the health services and schools directed toward eradication of the instillation of traditional medicines for the treatment of ocular infections, early referral, prevention of trauma, adequate surgical measures, and a better understanding of the pathology in some cases—for example, of cortical blindness—should be able to reduce considerably the incidence of blindness among young children in Malawi. A conjoint programme of the health and ophthalmology services aiming to reach a figure of 5 blind cases per 100 000 children within the period of 5 years is being established and will be further reported.

We thank Professor I. C. Michaelson, director of the Jerusalem Institute for the Prevention of Blindness, for his support and advice. Our thanks are due also to Mrs Sapao, head nurse of the department of ophthalmology, Queen Elizabeth Central Hospital, Blantyre, Malawi, and to Mr Buniani, clinical officer, ophthalmic assistant, in charge of the eye unit, Zomba Central Hospital, for their valuable help during this study.

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British Journal of Ophthalmology, 1977, **61**, 158

Book reviews

Vitreoretinal Disorders: Diagnosis and Management. By F. I. TOLENTINO, C. L. SCHEPENS, and H. MACKENZIE FREEMAN. 1976. Pp. 659, figs., tables, refs. W. B. Saunders, Philadelphia. (Eastbourne, Holt-Saunders) ($43·50)

The need for a comprehensive textbook on the subject of vitreoretinal disorders, of which the surgical management has developed remarkably over the past few years, is met by this new work, under the authorship of workers well recognised as pre-eminent in the field, who share the additional advantage of association with the same institution.

The first part of the book brings the reader up to date with advances in the knowledge of vitreous physiology and biochemistry, an essential basis on which to consider the broad spectrum of vitreous and vitreoretinal disorders, the description and discussion of which constitute the major portion of the book. The fourth part, which deals with vitreous surgery in all its aspects, provides the detailed description and critical commentary most likely to be of value to the specialised worker in this field.

The entire volume is written to give a full account of the subject, enhanced in each part by a critical and personal approach made possible only by the extensive clinical experience of the authors. The assessment of the appropriate instrumentation, the views expressed on the underlying pathology of vitreous and vitreoretinal disorders, and the cautious consideration of the value of currently popular methods of vitreous surgery exemplify this approach.

The excellent text is particularly well illustrated. Each chapter includes a full list of references, and the book can be confidently recommended to the aspiring worker in the field of vitreoretinal disease. The chapters on instrumentation and examination technique will be of special interest to postgraduate students seeking a practical introduction to this aspect of their curriculum.

J. R. HUDSON

Management of Ocular Injuries. By D. PATON and M. F. GOLDBERG. 1976. Pp. 381, 158 figs., 22 tables, bibliography. Saunders, Philadelphia, London, Toronto (£10·75)

This book is small enough to be carried easily and is written by two authors well known in the field of trauma, who write with authority. The style is refreshing, easy to read and understand. There is a tendency to use colloquial phrases rather than aiming at higher literary quality. It is very practical and allows quick reference by very useful tables throughout; it is also well illustrated.

Urgencies and emergencies are considered as well as injuries. For instance, central retinal arterial occlusion, acute glaucoma, orbital cellulitis, cavernous sinus thrombosis, gonococcal ophthalmia, acute iritis, giant cell arteritis, and retinal detachment are considered as urgent situations. Optic nearitis, ocular tumours, exophthalmos, chronic glaucoma, old retinal detachments, and squint with amblyopia are tabulated as semiurgent problems. The differential diagnosis of the blurred optic disc is discussed. There is a section on ocular infections related to injury which goes into more detail than would be expected from the title of the book and its preface.

There are some detailed criticisms. Basic equipment is described, including instruments which are very unlikely to be properly maintained in accident room conditions. They would need to be looked after by more specialised staff. The commonest site of intraocular foreign bodies (i.e., lying in the vitreous against the retina) is not indicated in text or diagram (p. 101–102). The EMI-scan is described as a non-radiographic technique (p. 119). The magnet test is advocated to determine magnetic properties, despite the availability of electronic detectors which can determine this without introducing the danger of an unnecessary movement of a foreign body. The magnet test can allow the mistaken diagnosis of a non-magnetic fragment if incarceration prevents the fragment from moving (p. 147). The overlapping trapdoor sclerotomy is not mentioned; the less satisfactory circumferential linear sclerotomy is advocated for the pars plana approach (p. 149). Greater reference to the value of ultrasonography and electrophysiology in assessment would be welcome (p. 209). The suggestion that a luxated lens can be kept in the anterior chamber by miotics is no longer widely held, and some means of instrumental fixation before surgical incision is more appropriate (p. 304).

In the context of the whole book these are minor criticisms. The text is very forward-looking with regard to the application of new instruments in the management of ocular trauma and reflects the many changes which have developed recently. There is an extensive bibliography but relatively few references to European work. It seems to cover American sources comprehensively.

This very manageable volume will have great value to all working in general or ophthalmic accident and emergency departments whether medical, nursing, or paramedical, and it is a source of clear-cut and up-to-date views.

M. J. ROPER-HALL

Nuclear Ophthalmology: Dynamic Function Studies in Intra-ocular Disease. By J. O'ROURKE. 1976. Pp. 156, figs, tables, refs. W. B. Saunders, Philadelphia ($10·50)

The author is both physicist and ophthalmic surgeon and combines these two disciplines to practical effect by the application of nuclear medicine techniques to the measurement of ocular physiology and pathology. This slender volume describes the author's own experience in selected techniques and does not discuss the work of others in related fields. An informative introduction describes the general principles of the use of radioisotopes in ophthalmic measurement. This is followed by detailed descriptions which include measurement of clearance from the anterior chamber, capillary exchange as measured by xenon-133 clearance and phosphorus-32 uptake by malignant melanomas. The book can be recommended for its practical value to workers in this field. NICHOLAS BROWN

Biométrie Oculaire Clinique (Oculométrie). By Y. DELMARCELLE, J. FRANÇOIS, F. GOES, J. COLLIGNON-BRACH, J. LUYCKX-BACUS, and H. VERBRAEKEN. 1976. Pp. 608, 192 figs., 116 tables, bibliography. Paris, Masson (250 fr).

This is a factual account of the dimensions of the eye, its adnexa, and contents as these relate to clinical practice. Apart from a simple account of the problems of biological measurement there is but little discussion of the reliability of the data presented or the problems of obtaining a specific ocular measurement. This somewhat detracts from the value of the book for those who are undertaking some new work in this field. However, as a book of reference it is excellent, and an extensive bibliography contributes much to its value. R. F. FISHER

Medical Ophthalmology. Edited by F. CLIFFORD ROSE. 1976. Pp. 574, figs., refs. Chapman & Hall, London (£15)

Thirty-five contributors, the large majority from London, have produced an up-to-date, well-indexed, comprehensive book on the most important aspects of non-operative ophthalmology. It is divided as follows: Part I, Diagnostic Aspects, pp. 1–68 (tests of visual function, fluorescein angiography, electrophysiology, radiology of unilateral proptosis); Part II, Neuro-ophthalmology, pp. 69–237; Part III, Inflammatory Disorders, pp. 238–338 (excluding pyogenic infections); Part IV, Vascular Disorders, pp. 339–429; Part V, Other Systemic Disorders, pp. 430–517 (diabetes, Graves's disease, blood disorders, cataract); Part VI, General Therapeutic Aspects, pp. 518–555 (genetics, pharmacology, adverse drug reactions). Each chapter starts with a useful list of topics covered and ends with references.

This entirely new book will be useful and not too large for candidates for higher degrees in ophthalmology and for any clinician, especially the ophthalmologist and neurologist, who requires a concise account of eye-related disease and its management. Reasons of cost probably explain the absence of colour plates, but some of the black-and-white illustrations could be improved. £15 seems reasonable for this handsome volume. The quickly accumulating new material on this subject will probably justify new editions every 5 to 10 years, which the multiple authorship should be able to achieve without too much difficulty. C. J. PHILLIPS

Year Book of Ophthalmology. Edited by W. F. HUGHES. 1976. Pp. 376, 73 figs., tables, refs. Year Book Medical Publishers, Chicago (£14)

The 1976 volume reviews the literature up to January 1976 and maintains its high standard of compression and clarity. In addition to the abstracts the editor summarises present trends and highlights important aspects. The section on vision, refraction, and contact lenses has an introduction by Jack Hartstein; the section on glaucoma has a chapter by Jeffrey S. Robin and Philip P. Ellis on developments in pilocarpine therapy; there is an introduction to the section on the lens by Samuel D. McPherson and to the section on the uvea by T. F. Schaegel; in the section on the retina Gerald A. Fishman discusses rhodopsin and visual excitation; and the section on neuro-ophthalmology is introduced by Michael E. Rosenberg. These chapters add to the character of the production, which can be read in small quantities over a prolonged period. It is, furthermore, an excellent source of references. S. J. H. MILLER

Notes

XXIII International Congress of Ophthalmology

Kyoto, Japan, 14–20 May 1978

This congress will be held in the Kyoto International Conference Hall. Official languages are English, French, Spanish and Japanese. Scientific programme will consist of reports on (1) ocular immunology and (2) retinal pigment epithelium. There will be round-table discussions on ocular toxicology, choroidal circulation, management of corneal diseases, optic neuropathy, pathology of visual cells, vitreous surgery, and infections of the eye. In addition there will be free papers.

There will also be symposia supported by the International Council. (1) The International Organisation Against Trachoma will meet on 16 May 1978. (2) The International Agency for Prevention of Blindness will meet on 17 May 1978. (3) The International Study Committee for Teaching and Postgraduate Continuing Education in Ophthalmology will meet on 19 May 1978. (4) The International Glaucoma Club will meet at the Nara Hotel, Nara, 8–11 May 1978.

Those who wish to present papers or films or to enter items of display in the scientific exhibition are requested to submit their application forms with an abstract on their paper, film, or display of 200 words or less in one of the official congress languages by 30 April 1977. Inquiries to the Secretariat, XXIII International Congress of Ophthalmology, c/o Simul International Inc., Kowa Bldg. No. 9, 1-8-10 Akasaka, Minato-ku, Tokyo 107, Japan. Telephone (03) 582-4224, Cable, SIMULCONFER.

International Symposium on Glaucoma

Kyoto, Japan, 12 and 13 May 1978

A symposium cosponsored by the Japanese Glaucoma Research Club and the International Glaucoma Club will be held in Kyoto, Japan, before the 23rd International Congress of Ophthalmology. Secretaries: Dr Y. Kitazawa and Dr M. Takase, Department of Ophthalmology, University of Tokyo School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan. Official language English. Those wishing to present papers are requested to send abstracts to the secretaries by 31 August 1977.

Semi-annual Oculoplastic Surgical Dissection Course

New York Medical College, Westchester County Medical Center, 18–21 May 1977

18 May, registration and Cosmetic Surgical Seminar; 19 May, Cosmetic Blepharoplasty, Blepharoptosis, Trauma Surgery; 20 May, Lid Reconstruction, Lachrymal Surgery, Orbital Reconstruction; 21 May, Entropion, Ectropion, Orbital Fractures, Lid and Orbital Tumours. Inquiries to Ms Tamkin, c/o Dr Pierre Guibor, 630 Park Avenue, New York, NY 10021, USA. Tel (212) 734-1010.

New Orleans Spring Fiesta Ophthalmology Seminar

New Orleans, Louisiana, 28–30 April 1977

The second annual seminar will be held at the Royal Orleans Hotel in the French Quarter of New Orleans, Louisiana, USA. It will be devoted to intraocular lens implantation and the management of its complications, including keratoplasty and vitrectomy. Live surgery will be demonstrated on the final day. Inquiries to Robert F. Azar, MD, 144 Elk Place, Suite 1501, New Orleans, Louisiana 70112, USA.

Phacoemulsification and Cataract Methodology

London, 4 to 6 May

The third international congress on Phacoemulsification and Cataract Methodology will be held at the Intercontinental Hotel, London, England. Enrolment will be limited to 550 individuals, and the registration fee (lunch included) is US$200 or sterling equivalent, payable to the International Ophthalmic Congress and posted to A. Cathcart, 82 Harley Street, London W1N 1AE.

Oculoplastic Surgical-dissection Course

New York, 18 to 21 May

The ophthalmology department of the New York Medical College—Westchester County Medical Center will be presenting an eye plastic surgical course every May and November of each year. The 18 to 21 May 1977 session will be orientated towards the ophthalmic plastic, ENT plastic, general plastic, and dermatologic plastic surgeon. Cosmetic blepharoplasty, blepharoptosis surgery, lid reconstruction, lachrymal surgery, orbital reconstruction, entropion, ectropion, orbital fractures, and tumours will be covered. The objectives will be to provide the practising and resident surgeon with an integrated oculoplastic surgical course employing live surgery, videotapes, films, lectures, and participant's cadaver surgery. Faculty of over 25 authorities from various fields. For information write to Michael Dunn, MD, and Pierre Guibor, MD, 630 Park Avenue, New York, NY 10021, USA.

Eye Research

Japan, 22 to 25 May 1978

The third international congress of Eye Research will be held at Nemuno-Sato, Japan. For information write to Yoshizo Kikkawa, MD, Secretary, Organising Committee, Department of Ophthalmology, Osaka University Medical School, 1-1-50, Fukushima, Fukushima-ku, Osaka 553, Japan.

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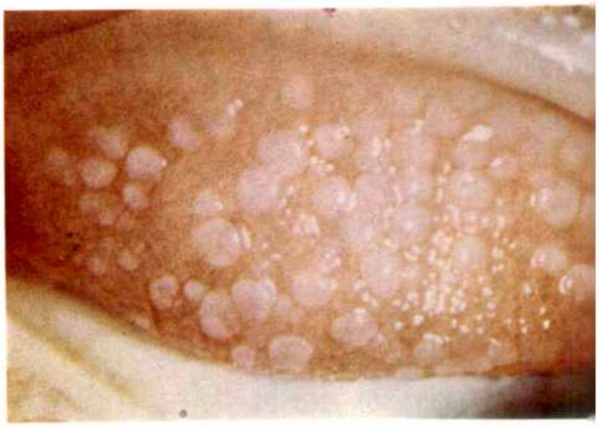
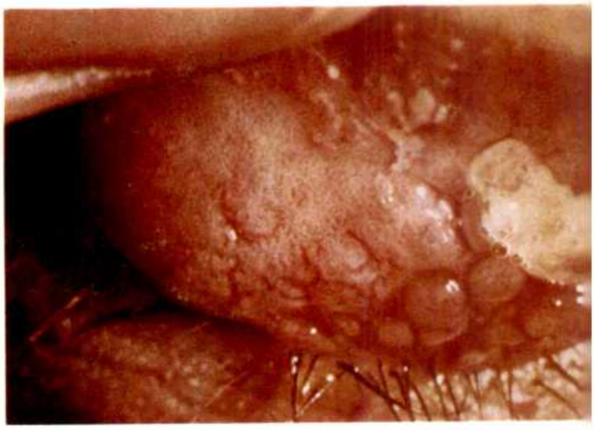
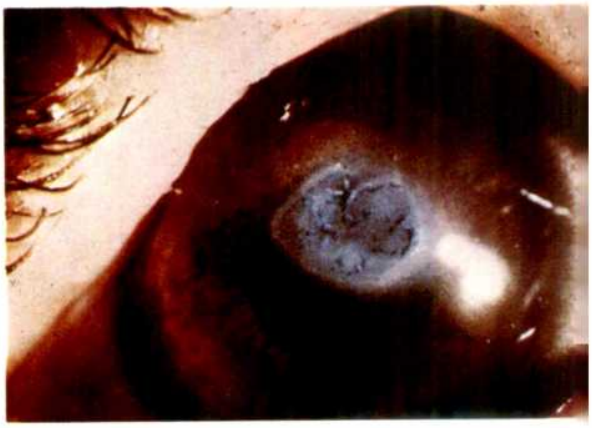


Right upper tarsus of adult patient with vernal kerato-conjunctivitis showing 'cobblestones' due to giant compound papillae.



Upper tarsal plate in active vernal disease. Note fine lace-like scarring and profuse mucopurulent discharge.



Indolent vernal corneal ulcer stained with alcian blue to demonstrate mucous deposition.

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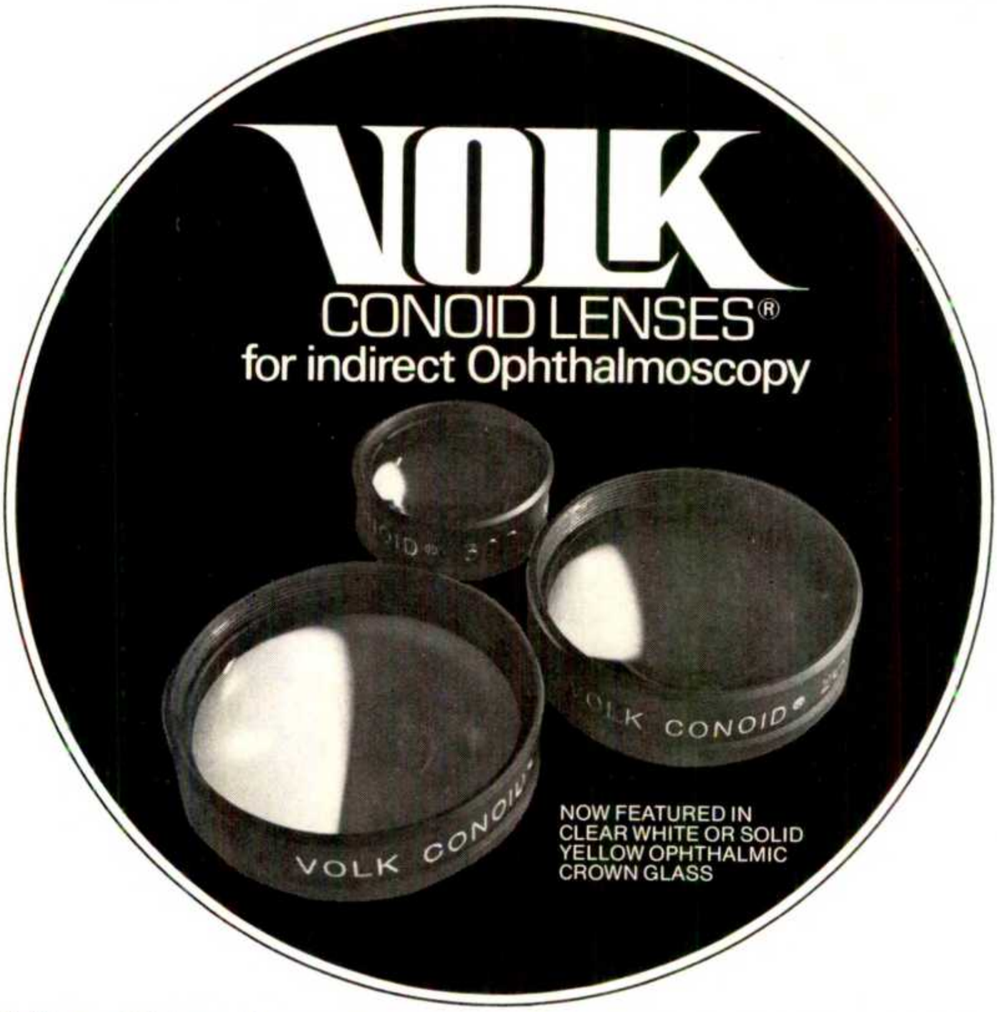

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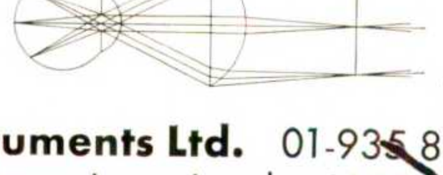

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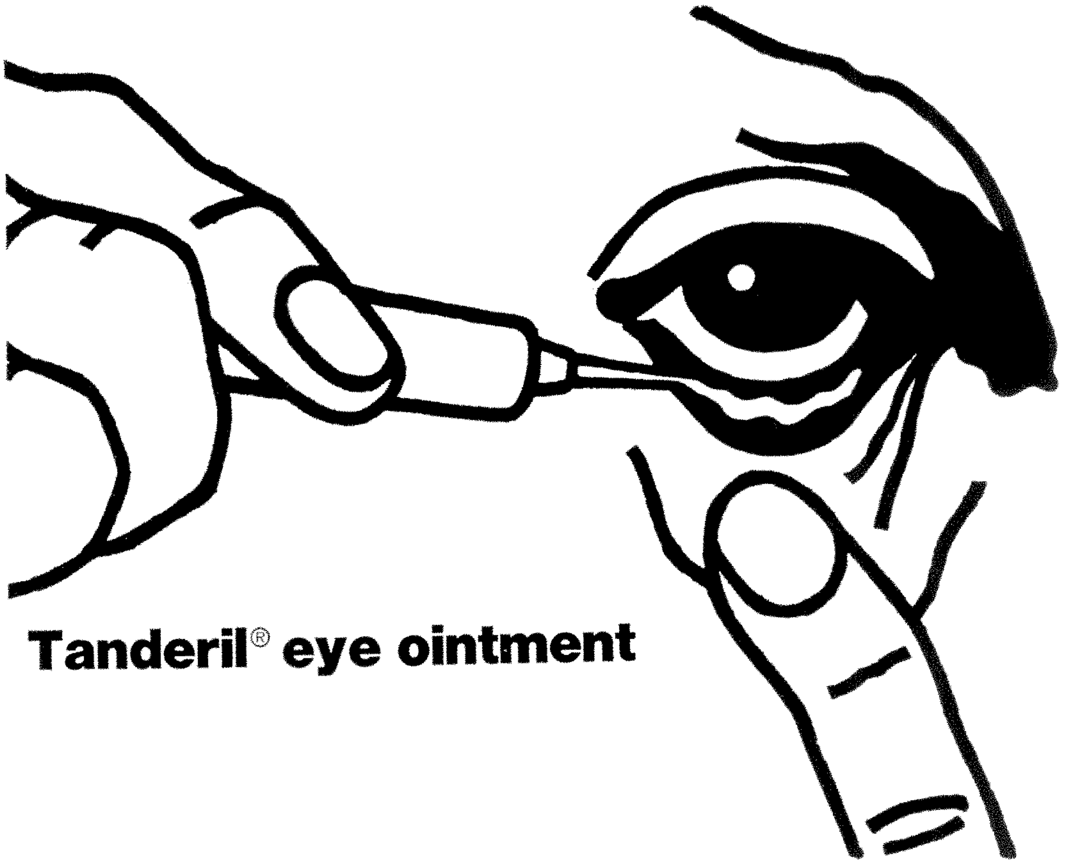

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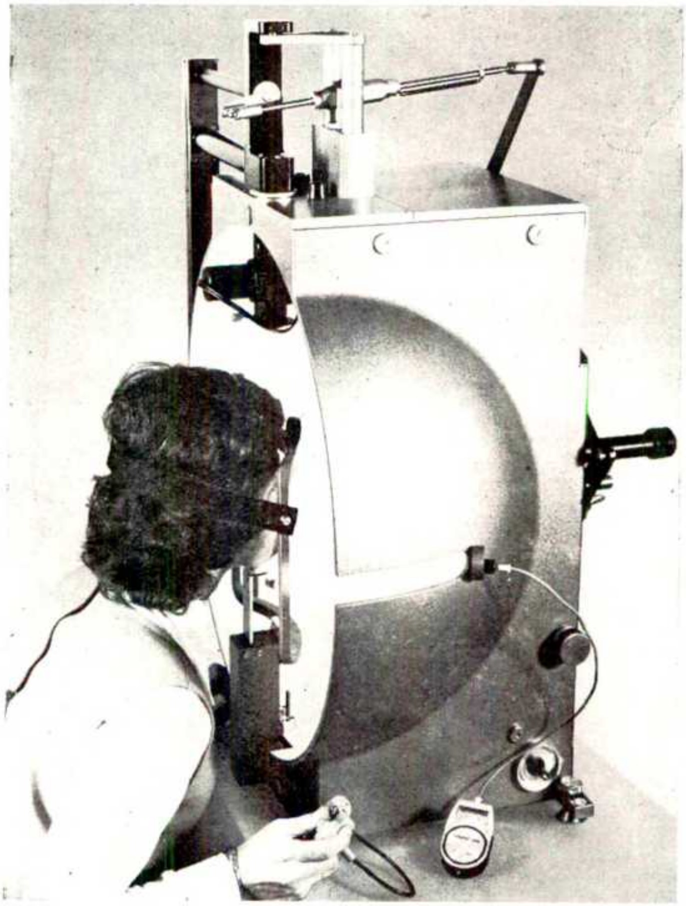

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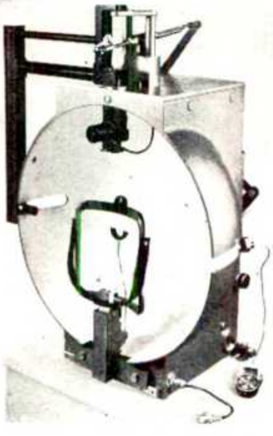

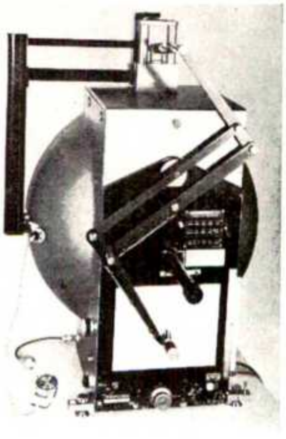

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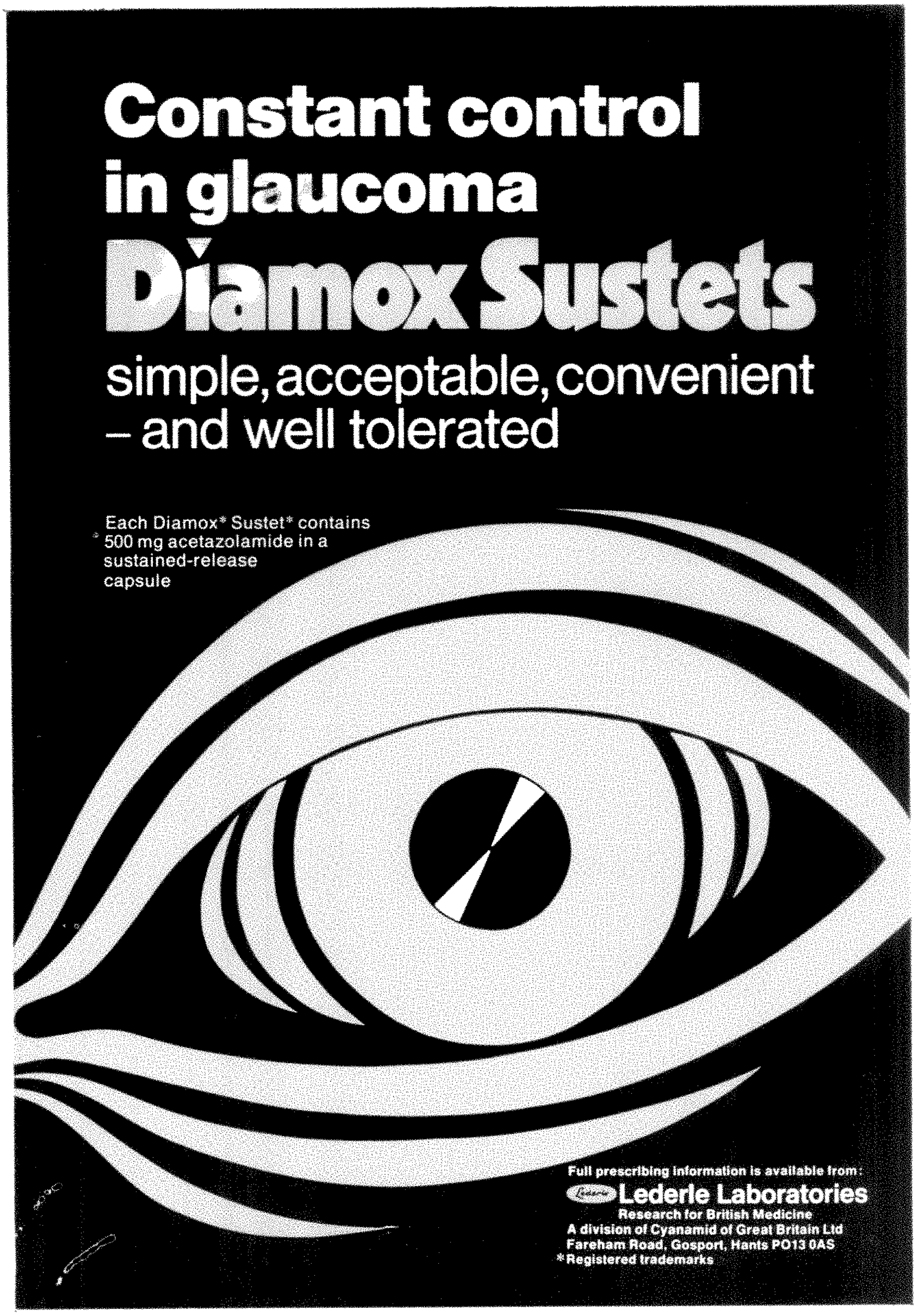

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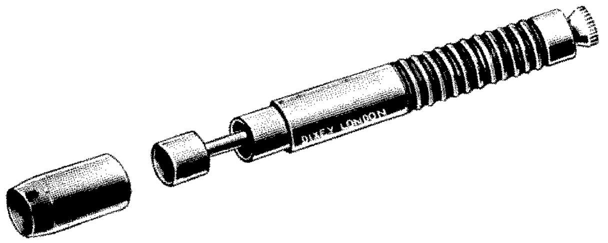

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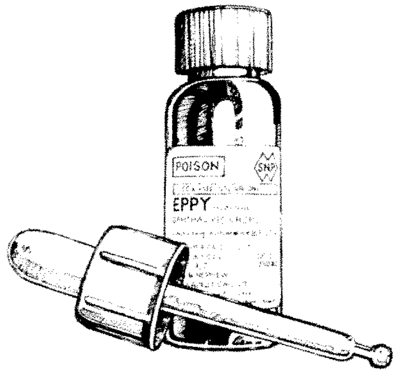

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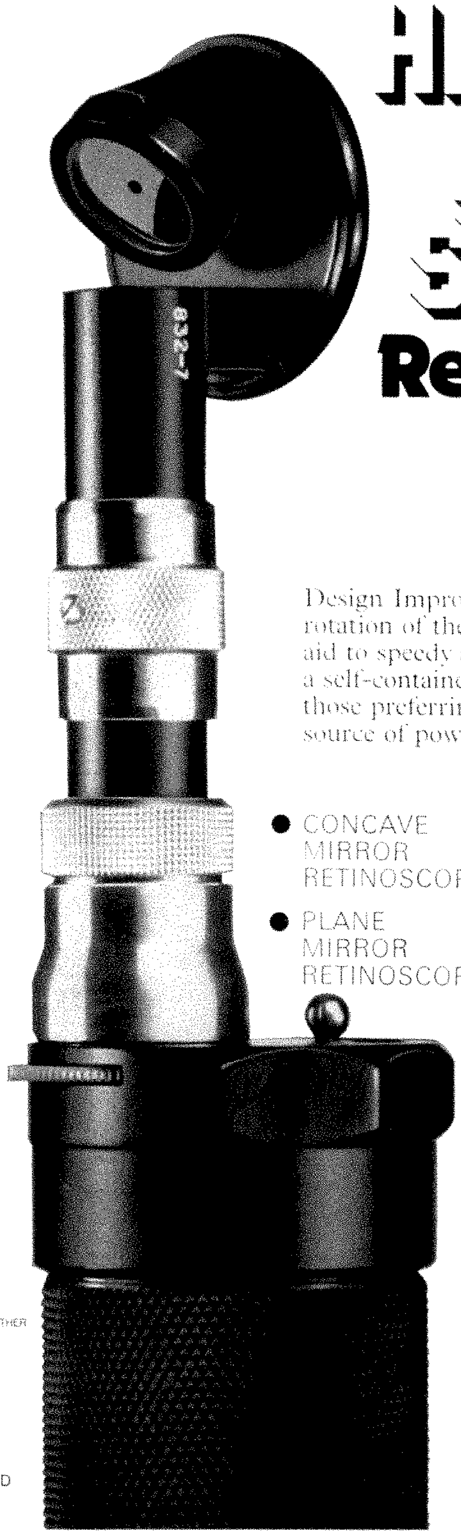

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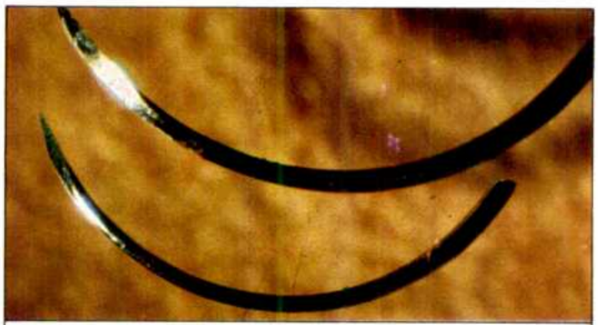

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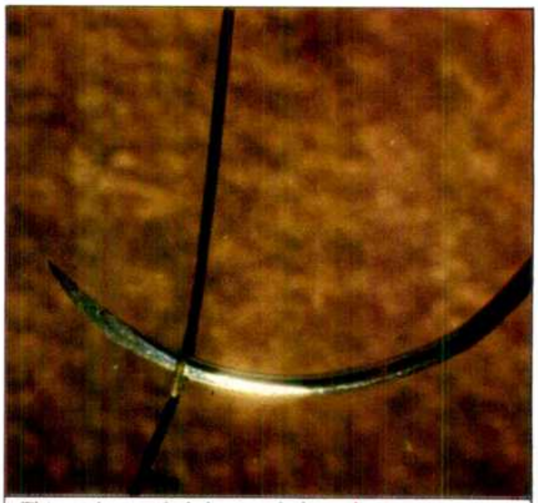

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Editorial: The retinal cotton-wool spot

The retinal cotton-wool spot has for many years excited the interest of ophthalmologists and histopathologists alike, and together they have defined through decades of careful work its clinical features, its associated diseases, and its structure and ultrastructure and have sought to explain its pathogenesis.

Familiar to generations of students of ophthalmology, the cytoid body has been the structure of dominant interest in the histology of cotton-wool spots, and indeed it can now be seen that the elucidation of the ultrastructure of this body, a century after its first description, was the turning point from the period of purely descriptive morphology to the more dynamic concepts of today.

Cytoid bodies were first described by Heymann in 1856 (in collaboration with Zenker in a case of Bright's disease) and were thought to be degenerate ganglion cells, a view with which Virchow (1856) agreed. Müller (1858), however, claimed that they were swollen varicose nerve fibres, and this was subsequently proved by Leber (1915); so that over 60 years ago it was suspected that varicose nerve fibres were basic components of the cotton-wool spot. Unfortunately, subsequent work tended to confuse rather than clarify this issue, it being suggested that cytoid bodies were 'moulded exudates' or 'non-specific deposits of acellular origin', the outer zone being precipitated ground substance and the inner zone fibrin or fibrinoid material. A further suggestion was that they represented glial degeneration (Verhoeff, 1921).

A return to the correct line of thought, however, was provided by Wolter (1959) when by silver staining of the retina he again showed cytoid bodies as terminal swellings of interrupted nerve fibres, and he pointed out their location on the distal stump in connection with the ganglion cell, whereas the proximal axon soon became atrophic. He also emphasised that the damage causing the interruption may be of any kind—a cut, compression, or ischaemia, for example. This was soon followed by a study of the pathology of cotton-wool spots and cytoid bodies in hypertensive retinopathy (Ashton and Harry, 1963), wherein it was established that the cotton-wool spot was causally related to focal ischaemia from arteriolar occlusion. The presence of localised axonal swellings in the affected zone was demonstrated and cytoid bodies proved to be sited at terminal axonal bulbs, which, in agreement with Wolter (1959), were thought to correspond to the bulbs of injured nerve fibres as described by Cajal (1913), who believed them to represent a combined process of degeneration and regeneration.

Further advances were made by Ashton and Harry (1963), who showed for the first time that the swollen nerve fibre of the cotton-wool spot contained aggregations of mitochondria, dense bodies, vesicles, and granules and that the fully formed cytoid body additionally contained a 'pseudonucleus' consisting of an electron-dense mass of ill-defined particles, probably deriving from degenerate elements in the axonal bulb. The nature of the cytoid body now seemed clear, but the pathogenesis of the cotton-wool spot itself was still obscure, although focal ischaemia was almost certainly involved.

It was then found that cotton-wool spots could be produced experimentally by emboli, by injecting either latex spheres (Gay *et al.*, 1964) or glass ballotini (Ashton and Henkind, 1965) into the carotid artery. These findings led to an extensive clinicopathological study in which cotton-wool spots were produced in the pig's retina by similar injections of glass ballotini, thus providing perfect experimental conditions for correlating the clinical evolution of the lesions with their ultrastructural changes as seen in suitably fixed material (Dollery *et al.*, 1966; Shakib and Ashton, 1966). Their crucial finding in the present context was that the injured axons in the ischaemic area rapidly became swollen, and after a few hours those swollen axons at the periphery of the lesion became packed with mitochondria, dense bodies, and membranous whorls; a break then occurred in the axon, and the distal stump attached to the ganglion cell formed a bulb-like swelling ('torpedo' formation) which developed into a cytoid body, while the proximal fibre atrophied. The swollen axons in the centre of the lesion did not develop this aggregation of organelles, only those axons at its periphery. These authors concluded that axons from irreparably injured ganglion cells within the ischaemic zone underwent complete degeneration, whereas axons of unaffected or surviving ganglion cells developed the 'torpedoes'.

The fundamental question arose as to the origin of the massive aggregates of mitochondria and other organelles within the terminal axonal swellings, and it seemed likely that proliferation beyond the normal turnover of organelles had taken place. It was well established at that time that mitochondria, for instance, can replicate (De Robertis and Bleichmar, 1962), but whether they could proliferate locally at the axon terminal was not clear. Shakib and Ashton (1966) considered axonal flow as a possible explanation of the organelle aggregation, although such an entity in the retinal axons had still to be generally recognised (Taylor and Weis, 1965, in mouse; Rahmann, 1968; McEwen and Grafstein, 1968; Elam and Agranoff, 1971a, b, in goldfish; Hendrickson, 1969, in the monkey; Cuénod and Schonbach, 1971, in the pigeon; and Karlsson and Sjöstrand, 1968, in the rabbit).

There were, however, reports of similar axonal reactions in crush injuries of the sciatic nerve of guinea-pigs by Webster (1962), who suggested that the accumulations arose through migration and proliferation of the pre-existing mitochondria, and in transected spinal cords of rats by Schlote (1964), who concluded that they were 'formed at the place where they are found and do not represent the result of damming the axoplasm or migration of organelles only'. On the other hand Friede (1964) believed that the accumulation of substances in an axon swelling did not inherently indicate a changed rate of production by the nerve cell and could result from a confined local shift of axoplasm. It had also been known for some years that organelle flow within axons was bidirectional (Hughes, 1953; Miani, 1964; Lasek, 1967), and Zelena (1968), in demonstrating this in an isolated segment of sciatic nerve, concluded that these particles shifted towards the fibre ends and were deposited there, although he could not exclude a local proliferation of mitochondria by division or segmentation. Shakib and Ashton (1966) interpreted their own findings as more in favour of a proliferation of organelles within the axonal bulb, but in a later paper it was further suggested that organelles of the ganglion cells might migrate into the axonal swellings and later proliferate at these sites (Ashton, 1970). Thus the main unsolved question remaining at that time was not the nature of the cotton-wool spot but the source of the axoplasmic organelles in the terminal swellings. Subsequently, research into the whole problem of axonal transport developed rapidly, as was well shown in the review by Jeffrey and Austin (1973) and in the Editorial recently published in this journal. Within this work the interesting view was expressed by Martinez and Friede (1970), again in a study of transected sciatic nerves, that the local formation of organelles in the axon stump is unlikely, since the magnitude of the increased density of organelles would necessarily imply an enormous multiplication of mitochondria, which would be inconsistent with the finding of a relatively small uptake of labelled amino-acids into swollen axons. They were in favour of an active redistribution of axoplasmic organelles towards the axon stump.

Axonal flow, as followed by labelled leucine with autoradiography or scintillation counting, is also now receiving attention in ocular conditions, especially as regards the effects of raised or lowered intraocular pressure on flow from the retinal ganglion cells to the lateral geniculate nucleus (Anderson and Hendrickson, 1974) or to the optic nerve (Levy, 1974; Minckler *et al.*, 1976).

It is only very recently, however, that the role of axonal flow has again been considered in the case of cotton-wool spots. Beginning from purely clinical studies of fundi with retinal vascular occlusion McLeod (1975) deduced that axonal ischaemia in the retina results in the interruption of both orthograde and retrograde axon flow and that the dense white opacity of the cotton-wool spot is due to the aggregation of organelles on either side of the lesion; while centrally the ganglion cells become necrotic. He subsequently described, in terms of axoplasmic transport, the clinical manifestations of occlusion of the central retinal and posterior ciliary arteries (McLeod, 1976). Since neither axonal flow nor organelles nor ganglion cells are ophthalmoscopically visible, these views could be regarded only as interesting speculations based on circumstantial evidence interpreted in the light of microscopical studies in the literature, but the experimental work reported in the present issue (McLeod *et al.*, 1977) goes far to confirm them.

By occluding retinal arterioles of the pig with laser photocoagulation, both at the same time and after introducing labelled leucine into the vitreous, these co-workers have traced orthograde and retrograde axonal flow by autoradiography to the swollen axon terminals on both sides of the infarcts, and they have demonstrated by electron microscopy the accumulated organelles within them and the fundamental importance of the interruption of normal axonal flow. No evidence of atrophy of the distal axon was provided. The authors stress that, although ischaemia is the common cause of these lesions, they may develop from any other injury resulting in such axonal disruption, and they are not, therefore, to be regarded as synonymous with micro-infarction. This broader view of the pathogenesis of cotton-wool spots was also advocated by Ashton (1970).

There are, of course, dangers in interpreting these pathological lesions purely in terms of interrupted physiological flow, especially in circumstances as gross as ischaemia, wherein the ensuing chemical, physical, and bioelectrical disturbances might well be factors in determining the aggregation and proliferation of organelles; for instance, Shakib and Ashton (1966) found such aggregations also in intact fibres in the ischaemic zone. Nevertheless, this excellent work will surely stimulate further research into the role of axonal flow in neuroretinal disease, and it provides an instructive example of how new light can still be brought to bear on an old problem simply by informed clinical observation and deduction, backed by experimental confirmation, even in a field as fully explored as the ocular fundus.

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Immunopathology of the lens

I. Humoral and cellular immune responses to heterologous lens antigens and their roles in ocular inflammation

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SUMMARY In experimental rabbits heterologous soluble lens proteins consisting of α-, β-, and γ-crystallins were found to be antigenic; they stimulated a marked antibody response compared to a rather weak T-cell response. The serum antibodies to α-crystallins appeared first, to be followed by antibodies to β- and γ-crystallins in that order. The rabbits did not respond to heterologous γ-crystallins unless these were injected with Freund's adjuvant containing mycobacteria. Incomplete Freund's adjuvant (i.e., without mycobacteria) was found to be an inferior immunoaccelerator so far as lens antigens are concerned. The response to lenticular antigens in both magnitude and duration varied in different rabbits, which suggested to us the important role played by a central control mechanism involving the immune response (Ir) genes.

Some of the antibodies in potent lens antisera cross-reacted with mitochondria, endoplasmic reticulum (i.e., microsomes), contractile organelles, and cell nuclei. This explains for the first time at least in part the reasons for the widely observed phenomenon of the reactivity of lens antisera with ocular and extraocular structures. Antibodies to soluble lens proteins as detected by immunofluorescence and immunoperoxidase techniques were shown to be of the IgG class. Systemic heterologous immunisation followed by discission of the lens does not lead to the typical changes of phakoallergic endophthalmitis in the rabbit.

Interest in the antigenicity of the mammalian lens and its role in the production of autoimmune lesions in the eye appears to have originated with the study by Uhlenhuth (1903) in which rabbits were immunised with repeated doses of bovine lens material. Precipitating antibody was produced which reacted with lens extracts from many species. It did not react with bovine serum, however, which led to the general conclusion that the lens antigen, though not species-specific, was largely organ-specific.

This view prevailed for several decades among experimental ophthalmologists (Hektoen, 1922; Halbert *et al.*, 1957; Takata *et al.*, 1964), and even now in most textbooks on general medicine and immunology lenticular antigen is still regarded as a typical example of organ specificity. It is well established, however, that proteins resembling lens material are found not only in other ocular tissues but also in almost every organ of the body.

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Antigenic specificity of the lens

It is believed that the lens proteins evolved in the most primitive vertebrates (i.e., Agnatha) about 450 million years ago and have been transmitted intact to all vertebrates (Manski *et al.*, 1960). In a study of the immunological relationships of the lens in different phyla Halbert and Manski (1963) showed that the earliest vertebrate antigens, as represented in the lamprey, have been transmitted unchanged throughout all the more recent phyla. New antigens added at a later period of evolution have similarly but less consistently been transmitted to subsequent phyla. This tendency for the original antigen to persist through the millions of years represented by the range of phyla involved is probably a reflection in part of the isolation of the lens from the vascular system (Glynn and Holborow, 1965).

A number of investigators have reported that the lens antigens are present not only in other ocular structures (e.g., the iris, the retina, the cornea, the vitreous, and the aqueous humour) but also in extraocular tissues such as the brain, the skin, the skeletal muscles, the liver, and the renal glomeruli (Hektoen, 1922; Rao *et al.*, 1955; Maisel and Harmison, 1963a, b; Nozaki *et al.*, 1963a, b; Perkins and Wood, 1963; Zwaan, 1963; Cate, 1964; Mehta *et al.*, 1964; Rathburn *et al.*, 1971; Bours and Doorenmaalen, 1972). It is not surprising, therefore, that Campbell *et al.* (1968) found about 2 dozen electrophoretically distinct antigenic components within the lens, that all other tissues examined contained some antigenic determinants similar to those found in lens proteins, and that all of the major classes of lens proteins contained cross-reacting groups.

It is clear, therefore, that the so-called organ specificity of the lens is the result of a unique selection of antigens genetically available, any one of which may be found in other tissues, rather than being due exclusively to the possession of some specific protein restricted to the lens (Clayton *et al.*, 1968). Why the lens should contain so many different antigens and why they should be so widely distributed in nature can be appreciated only if the embryology and the fine structure of this largely and apparently acellular organ is critically examined.

Development of the lens and the distribution of its antigens

As soon as the optic vesicle, which develops as an extension from the anterior region of the neural tube, reaches the surface ectoderm at about the 4 mm stage in the human embryo, changes begin to occur under the influence of an inducer, which involves a thickening of the epithelium to form the lens plate that later invaginates to form the lens vesicle. From this vesicle the lens is ultimately evolved by the growth of constituent cells which first fill the cavity and then increase the size of the embryonic lens by subsequent multiplication of the epithelium in the equatorial region. The hexagonal cells are laid down in layers, the old ones being pushed towards the centre in the embryo, and the process continues throughout postnatal life. The older cells, being elongated, are now called lens fibres. They collect in the centre of the lens to form the nucleus, which gradually grows in size from a small embryonic structure through fetal, infantile, and adult forms, but retains all the antigenic components synthesised during these periods because of its nonvascularity and a generally slow turn-over of lens protein.

The anterior surface of the lens is covered by epithelium, which has a somewhat granular cytoplasm and contains the usual organelles (albeit in smaller numbers), including rough endoplasmic reticulum, mitochondria, ribosomes, Golgi complexes, microtubules, and microfilaments. The epithelium in the equatorial region, however, contains more fibrillar cytoplasm and chains of polyribosomes and elements resembling lysosomes. The cortical lens cells (i.e., the lens fibres) found immediately under the equatorial epithelium also contain all the cytoplasmic organelles, including microtubules; their number is greatly reduced, however, the cytoplasm becoming fibrillar and the nucleus markedly flattened. In the deeper cortex the morphology of the lens cells is totally altered. The organelles disappear progressively and the cytoplasm becomes amorphous owing to the accumulation of homogeneous granular material. The cell nucleus breaks up into small fragments, and the nuclear envelope is no longer discernible (Hogan *et al.*, 1971). The entire lens mass may be compared with a community graveyard containing the remains of several generations of lens fibres. It is not surprising, therefore, that it should contain a conglomeration of antigenic components associated with the cytoplasm and the nucleus.

The lens should not be simply regarded, however, as a graveyard, because all these changes have an evolutionary purpose and are essential for the transparency of the lens where active metabolism goes on throughout life (Heyningen, 1969) through gene repression and activation mechanisms directed towards the production of proteins, which do not oxidise readily to form insoluble components, thus maintaining the essential transparency of the lens.

Lens proteins: nature and classification

The lens proteins account for 35% of the lens mass, a higher concentration of protein than in any other tissue of the body.

Morner (1894) was the first to attempt fractionation of the various proteins of the lens, and he arbitrarily divided them into 4 types. After homogenisation and centrifugation the water-insoluble fraction was called the 'albuminoid'. The supernate was treated with tenth-normal acetic acid and the protein which precipitated at pH 5, he called α-antigen. What was left in solution was partially precipitated with a saturated solution of magnesium sulphate, and the precipitate was called β-antigen. The protein remaining in solution at the end of this procedure was mistakenly called 'albumin'.

This classification was modified 3 decades later by Burky and Woods (1928), who showed that the soluble proteins of the lens after initial precipitation of α-crystallin at pH 5 could be further precipitated by increasing the pH to 6 to obtain β-crystallin. What was then left in the solution was not 'albumin', as Morner thought, but contained another lens protein which they obtained as γ-crystallin by precipitation with 50% saturated ammonium sulphate. These workers also found that Morner's 'albuminoid' was not an immunochemical entity but consisted of crystallins, mainly the α-fraction, which had become insoluble for some unknown reason (Woods and Burky, 1927).

After the introduction of electrophoretic techniques attempts were made to introduce a new classification for the lens antigens on the basis of their surface charge and therefore their electrical mobility. The fast moving fraction of the lens protein was called α-crystallin (Hesselvik, 1939; Viollier *et al.*, 1947; François *et al.*, 1954), the slow moving fraction at pH 7 or above was γ-crystallin (Resnik *et al.*, 1960), and the proteins of intermediate mobility were regarded as β-crystallins.

It was soon realised, however, that the lens homogenate contained several distinct proteins differing in their solubility at a different pH, in their electrical charge, and in their molecular size. It was Bjork (1961) who first attempted to separate and purify the various lens proteins on the basis of their molecular size using the new technique of gel filtration. This simple procedure is probably the best and most effective for the isolation of any single group of proteins from the complex mixture present in the vertebrate lens and has been widely used by subsequent investigators to purify the various α-, β-, and γ-crystallins.

The soluble lens proteins are now generally separated from each other by filtration on DEAE-cellulose by consecutive elution with buffers of increasing concentration; 0·002 M-phosphate elutes the γ-crystallin fractions, 0·03 M the β-crystallin fractions, 0·05 M a mixture of α- and β-crystallins, and finally 0·4 M-phosphate elutes α-crystallins.

α-CRYSTALLINS

The α-crystallins have the highest molecular weight and the greatest positive charge at alkaline pH and therefore move fastest on electrophoresis. Although they exist as variable polymers, α-crystallins consist of 4 different polypeptide chains. The A_1 chain (i.e., the acidic polypeptide) is derived from the A_2 chain, and the B_1 (i.e., the basic polypeptide) is derived from the B_2 chain. The molecular weight of A chains is approximately 19 500 and that of B chains 22 500 (Spector *et al.*, 1971). The α-crystallins have blocked terminal amino groups which are acetylated and contain methionine. It is of interest to note that there are few proteins which are N-acetylated, and the list includes tobacco mosaic virus, carp haemoglobin, histone IV of calf thymus, basic protein from the human brain, high sulphur wool protein, and human heart cytochrome C (Croft, 1973). Human α-crystallins have a much lower molecular weight, however, than calf α-crystallins and appear to increase in concentration with age; they represent about 40% of the total soluble lens protein in old persons (Spector *et al.*, 1973).

β-CRYSTALLINS

The β-crystallins are not as well defined, however, and apparently consist of groups of proteins with molecular weights ranging from 5×10^4 to 2×10^5 (Armand *et al.*, 1970). The β-crystallins contain many polypeptide chains, some of which appear to be present in aggregates. Shapiro (1968) has reported that this protein group contains 3 different-sized polypeptide chains of molecular weights 21 000, 23 000, and 29 000. These proteins have a relatively higher thiol content than α-crystallins. A high thiol content makes a protein susceptible to oxidation, which leads to the appearance of disulphide bonds and the formation of insoluble components. This process is normally kept under control in the lens by substances such as glutathione.

γ-CRYSTALLINS

The γ-crystallins are the least positively charged proteins at an alkaline pH and therefore move very slowly on electrophoresis. They consist of a number of closely related proteins, all containing single polypeptide chains with molecular weights of about 19 000 (Croft, 1971). They are rich in thiol groups (which means they become insoluble very easily) and unlike α-crystallins are not N-acetylated and have free N-terminal amino-acids. Human γ-crystallins behave like cryoproteins. The protein tends to precipitate from its solution at 4°C but readily redissolves on warming. These proteins are responsible for the phenomenon of 'cold cataract' (Zigman and Lerman, 1965). The γ-crystallins have an unusual amino-acid composition: alanine and lysine are rare, arginine and tyrosine abound. Furthermore, γ-crystallins appear to be relatively primitive proteins in terms of evolution and development, the trend being towards the synthesis of lens proteins of lower isoelectric point with improved oxidative stability.

It is now evident that the 4 lens antigens which Morner (1894) described as distinct chemical entities are in fact several families of proteins which are grouped together because of their solubility characteristics, molecular sizes, and surface electric charges at a particular pH. It is not surprising, therefore, that Manski (1973) now believes that the terms α-, β-, and γ-crystallins are as outdated as the term 'globulins'. There are now immunochemical data about the different β- and γ-crystallins which allow us to classify each of the lens proteins in their β- and γ-crystallin families. In the bovine lens there are at least 7 different γ-crystallins, some of which are concentrated in the nucleus and others in the cortex (Croft, 1973).

In addition it is now well known that human as well as animal lenses contain pre-α-crystallins and crystallins which show electrophoretic mobility between β- and γ-crystallin; the latter are called βs-crystallin. The βs-crystallin, like γ-crystallin, is a low molecular weight protein, and in human cataractous lenses, when the γ-crystallins become insoluble, the βs still remain in solution (Croft, 1973; Vincentiis *et al.*, 1975). It should be realised, however, as Harding (1972) has recently pointed out, that most of the insoluble albuminoids in normal and cataractous lenses are in fact artefacts of oxidation. He has shown that, if lenses are homogenised in the absence of oxygen in an atmosphere of nitrogen alone, most of the proteins stay in solution.

In addition to the various crystallins the lens also contains other antigenic substances such as nucleoproteins, lipoproteins, glycoproteins, the various enzymes associated with cellular transport and metabolism, and the structural proteins associated with the lens capsule (Kuck, 1969).

The findings in the classical study of Uhlenhuth (1903) of a positive humoral immune response to heterologous lens antigens has been repeatedly confirmed by Hektoen (1922), Woods and Burky (1927), and many others by using simple liquid phase precipitation and complement fixation tests. The agar-gel diffusion technique of Oudin (1947) was first utilised by Rao *et al.* (1955), who were able to show that heterologous lens antisera contained antibodies to at least 6 different antigenic determinants. Several more antigenic determinants were detected when Manski *et al.* (1960) popularised the immunoelectrophoretic methods for the study of lenticular antigens.

In earlier studies the lenses were injected without any adjuvants, which meant higher doses and prolonged immunisation before a good antibody response was detected. Furthermore, the immune response in different animals was very variable and unpredictable, probably owing to innate unresponsiveness. Freund's complete adjuvant, which consists of water-in-oil emulsion with tubercle bacilli (Freund and McDermott, 1942) is a powerful immunoaccelerator. Apart from producing a depot effect leading to a prolonged antigenic exposure this adjuvant appears to break down the state of immune tolerance by a non-specific direct stimulation of T-lymphocytes. It can be recalled that T-lymphocytes are required not only for cellular immunity but also through the mechanism of cellular cooperation for a good antibody response by the cells of the B-lymphocyte series. An incomplete Freund's adjuvant does not contain mycobacteria but acts as a good immunoaccelerator in many situations. Its role in lens antibody responses, however, has not been reported so far.

A review of the literature further suggested to us that the following aspects of humoral and cellular immune responses to heterologous lens antigens have also not been adequately investigated.

(1) Although agar-gel diffusion (i.e., Ouchterlony test), immunoelectrophoresis, complement fixation, and haemagglutination tests have been widely used, recent techniques such as immunofluorescence and immunoperoxidase methods have not been properly applied to the study of lens antibodies. Enough data are not, therefore, available to decide which techniques are best suited for the diagnosis of experimental or clinical phakoallergic* endophthalmitis. Immunofluorescence and immunoperoxidase techniques have the added advantage of localising the site of antigen-antibody reaction at microscopical levels.

(2) We are not aware of any study in which the kinetics of the humoral immune response to the same heterologous lens antigen in saline with incomplete and complete Freund's adjuvant have been examined and where the relative merits of agar precipitation, haemagglutination, immunofluorescence, and immunoperoxidase methods have been critically compared.

(3) It is now known that antibodies in man and most mammals belong to several distinct classes of immunoglobulins, and the various serological techniques which have been used in the past to detect lens antibodies demonstrate preferentially one class of immunoglobulin. For example, the agar precipitation test detects mainly high-affinity IgG, the haemagglutination test mainly IgM, and the complement fixation test only the complement-fixing IgG and IgM. Immunofluorescence and immunoperoxidase methods on the other hand can in addition detect IgD and IgE antibodies. With monospecific antisera it should now be possible to be certain which immunoglobulin is mainly involved in lens immunity.

(4) It has only recently become clear that delayed tissue allergy is produced by thymus-derived T-lymphocytes, and evidence for such a state can be obtained by a simple *in-vitro* technique in which thymus-dependent lymphocytes in tissue culture from a sensitised animal undergo blastic trans-

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* The term phakoallergic endophthalmitis has been used throughout the text as a preferred alternative to such terms as lens-induced uveitis, endophthalmitis phakoanaphylactica, or phakogenetic endophthalmitis. The reasons for this are discussed in a separate communication.

formation when challenged with appropriate antigen. The transformation can be observed directly by examination of stained preparations or measured in terms of radioactive thymidine uptake (Ling and Kay, 1974). We are not aware of any study in which the lymphocytes of animals sensitised with heterologous lens antigens in saline, and with incomplete and complete adjuvants, have been examined and the response correlated with antibody levels.

(5) Although the cross-reactivity of lens antisera with ocular and extraocular tissues is well known, the microscopical localisation of these cross-reacting antigens has not so far been seriously attempted.

The present investigations were therefore carried out in an attempt to bridge some of the gaps in our knowledge concerning the antigenicity of the lens and the nature of the immune response to lens proteins and its role in ocular inflammation.

Material and methods

The experiments were performed on healthy New Zealand albino adult rabbits, litter mates being used where possible. Rat and guinea-pig soluble lens proteins in saline, or with incomplete and complete Freund's adjuvant, were injected separately into 6 groups of rabbits. The injections were given intramuscularly at different sites at 10-day intervals. Each injection contained 6 mg of soluble lens protein as measured by the technique of Lowry *et al.* (1951). The animals were bled on the day of initial immunisation and also at the time of subsequent injections in order to study the sequential antibody response. The sera were deep-frozen and stored in aliquots. After the thirteenth immunising dose the animals were skin-tested, and the site was biopsied 48 hours later. The animals were anaesthetised with intravenous sodium pentobarbitone and discission of the right lens was performed with a Ziegler's knife using a dissecting microscope. They were killed a week later, and blood was collected from the heart into a preservative-free heparinised container for the lymphocyte transformation test. Both eyes were enucleated for microscopical examination. Two groups of control rabbits received intramuscular injections of complete or incomplete adjuvant only and blood was tested for evidence of humoral and cellular immunity to lens protein. In another group of rabbits lenses were needled without previous immunisation and the eyes examined histologically one week later for any evidence of inflammation.

IMMUNOLOGICAL INVESTIGATIONS

Agar-gel diffusion (Ouchterlony test) was performed at room temperature on glass plates coated with 1·5% agar in barbitone buffer (pH 8·2). The plates were washed 5 days later, first in 3% saline and then in distilled water, and after drying at 37°C were stained with 0·1% nigrosine.

Immunoelectrophoresis and Osserman tests were performed on 10×10 cm agar plates coated with 1·5% agar in barbitone buffer (pH 8·2, I=0·05). The electrophoresis tank (Shandon U77) contained barbitone buffer of pH 8·6 (I=0·075). The electrophoresis was carried out at a constant current (10 mA/plate) for 3 hours according to the methods described previously (Rahi and Chignell, 1975) as a modification of the techniques of Grabar and Williams (1953) and Scheidegger (1955). The plates were washed, dried, and stained in a way similar to those described for the Ouchterlony test.

Passive haemagglutination test.—The technique used for coating the formalised sheep red cells with lens antigens was essentially the same as described by Cruickshank *et al.* (1975) for thyroid antigens. 2 mg of preabsorbed rabbit or human lens protein in phosphate buffer saline (pH 7·2, 0·15 M) was added to each millilitre of tanned red cell suspension and incubated for 30 minutes. The red cells thus sensitised were carefully washed with the buffer containing 1% normal rabbit serum, which was previously heat-inactivated and adsorbed. The fluid concentration of red cells was adjusted to 1·25%. Sera from immunised and control animals were inactivated and preadsorbed with unsensitised sheep red cells. The test was performed on the microtitre assay system (Cooke Laboratory). Proper controls were set up with sensitised cells in buffer alone and with non-immune serum obtained from the animals before initial immunisation. Controls were also set up using unsensitised cells with and without antiserum.

Immunofluorescence test.—The indirect immunofluorescence test was performed by a standard technique. A Zeiss epifluorescence microscope equipped with a fluorescein isothiocyanate (FITC) interference filter was used for the present study. Frozen sections of a composite block consisting of liver, kidney, stomach, parotid, and diaphragm from a rat and stomach from a mouse were used to detect cross-reacting antibodies in lens antisera. Rabbit, guinea-pig, and rat eye sections were used to detect an immune reaction not only with the lens but also with other ocular structures. The sera were tested at an initial dilution of 1:5, and both polyvalent (Wellcome) and IgG-specific (Dako) anti-rabbit immunoglobulin labelled with FITC were used for the present study.

Immunoperoxidase test.—Frozen sections of the composite blocks and of the eyes similar to those required for immunofluorescence studies were used for immunoperoxidase staining. Sections were first treated with 1:20 normal pig serum to block non-specific reactions and then with 1:10 lens antiserum. After washing, peroxidase-labelled anti-rabbit IgG serum, raised in pigs (Dako) and diluted 1:50, was put on these sections which were incubated and later washed in a bath equipped with a magnetic stirrer. The slides were then incubated for 10 minutes in freshly-prepared diaminobenzidine tetrahydrochloride (DAB) reagent in a concentration of 6 mg/10 ml Tris saline and containing 2 drops of 10 vol. solution of hydrogen peroxide. The sections were washed well in distilled water and counterstained with haematoxylin. Fresh frozen sections were stained separately for endogenous peroxidase. Controls were also set up to detect any non-specific reaction with peroxidase-labelled antisera alone.

Lymphocyte transformation test.—The lymphocytes were separated from the rabbit blood by the Ficoll-Hypaque technique (Fotino *et al.*, 1971). 10^6 lymphocytes were cultured in 1 ml TC 199 prepared in HEPES buffer and enriched with 10% heat-inactivated fetal calf serum. Several such cultures were set up in Sterilin tubes. To each of the experimental tubes 0·1 ml of 1% lens solution passed through a millipore filter was added, and 48 hours later 2 μCi tritiated thymidine (30 000 mCi/mmol) was added to each tube and mixed. The control tubes were also treated with the same amount of radioactive isotope. After centrifugation, the proteins in the cellular deposits were precipitated with trichloracetic acid and filtered on glassfibre filter papers, which were transferred to scintillation vials and air-dried. The vials were counted after the addition of 10 ml toluene-based scintillation fluid, in a Packard tricarb liquid scintillation counter.

Results

Sera from all animals collected before immunisation were negative for lens antibodies as shown by simple agar diffusion, immunoelectrophoresis, passive haemagglutination, immunofluorescence, and immunoperoxidase tests. Antibodies to heterologous lens proteins appeared on the 10th day of immunisation when antigen was given either with complete or incomplete Freund's adjuvant, whereas when antigen was given in saline alone antibodies were not detectable until 30 days. The final haemagglutinin titre after 75 days of immunisation rose to 1:81 290 with complete adjuvant; when the antigen was injected with incomplete adjuvant the plateau was reached much earlier, and the haemagglutinin titre on the 75th day rose only to 1:20 840, a level which was the same as when saline homogenate only was used (Tables 1, 2, and 3).

In general, rabbits reacted better against guinea-pig lens antigens than against rat lens antigens, the number of precipitin lines being higher with the antisera produced against the former species.

At least 7 distinct antigenic substances were found in heterologous lens homogenates both by the Ouchterlony and immunoelectrophoretic methods (Fig. 1). At least 2 precipitin lines were seen in the

Table 1 *Antibody response in a rabbit injected with heterologous soluble lens proteins in Freund's complete adjuvant*

Methods of antibody detection	*Days after initial immunisation*						
	10	*20*	*30*	*40*	*50*	*60*	*75*
Gel diffusion (Ouchterlony)	−	±	+	+	+	+	+
Immunoelectrophoresis	−	+ (α)	+ (α, β)	± (α, β)	+ (α, β)	+ (α, β, γ)	+ (α, β, γ)
Passive haemagglutination	± (1:10)	+ (1:640)	+ (1:5120)	+ (1:10 240)	+ (1:20 240)	+ (1:20 480)	+ (1:81 290)
Indirect immunofluorescence	±	+	+	±	+	+	+
Immunoperoxidase	*	+	+	+	+	+	+

+ Positive; ± weak positive; − negative; * not tested; (α, β, γ) = antibodies to α-, β-, and γ-crystallins

Table 2 *Antibody response in a rabbit injected with heterologous soluble lens protein in Freund's incomplete adjuvant*

Methods of antibody detection	*Days after initial immunisation*						
	10	*20*	*30*	*40*	*50*	*60*	*75*
Gel diffusion (Ouchterlony)	−	+	+	+	+	+	+
Immunoelectrophoresis	−	+ (α)	+ (α, β)	± (α, β)	± (α, β)	+ (α, β)	+ (α, β)
Passive haemagglutination	± (1:40)	+ (1:640)	+ (1:1280)	+ (1:2560)	+ (1:5020)	*	+ (1:20 480)
Indirect immunofluorescence	±	+	+	+	+	*	+
Immunoperoxidase	*	+	+	±	+	*	+

+ Positive; ± weak positive; − negative; * not tested; (α, β) = antibodies to α- and β-crystallins

Table 3 *Antibody response in a rabbit injected with heterologous soluble lens protein without adjuvant*

Methods of antibody detection	*Days after initial immunisation*						
	10	*20*	*30*	*40*	*50*	*60*	*75*
Gel diffusion (Ouchterlony)	−	−	−	−	−	+	+
Immunoelectrophoresis	*	*	*	*	+ (α)	+ (α, β)	+ (α, β)
Passive haemagglutination	−	−	+ (1:10)	+ (1:640)	+ (1:1280)	*	+ (1:20 480)
Indirect immunofluorescence	*	*	±	−	−	*	−
Immunoperoxidase	*	*	*	−	−	*	−

+ Positive; ± weak positive; − negative; * not tested; (α, β) = antibodies to α- and β-crystallins

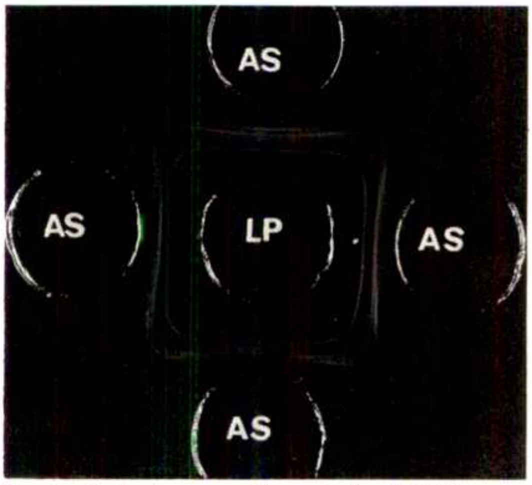

Fig. 1 *Ouchterlony test: The central well (LP) contains soluble lens proteins from a guinea-pig. The peripheral wells (AS) contain sera from 4 rabbits immunised with heterologous soluble lens proteins in Freund's complete adjuvant. There are a varying number of precipitin lines*

α-region, 3 in the β-region, and 2 in the γ-region when guinea-pig lens was injected with complete Freund's adjuvant. The antibodies to α-crystallins appeared several days before those to β-crystallins; antibodies to γ-crystallins developed 60 days after immunisation and then only when the antigen was injected with complete adjuvant. When the antigen was given in saline or with incomplete adjuvant (i.e., without mycobacteria), antibodies to γ-crystallins were not detectable even 75 days after continuous immunisation (Fig. 2).

The level of the immune response in the three groups of rabbits varied in a manner depending on the use of Freund's adjuvant. The kinetics of the antibody response to heterologous (mammalian) lens antigen in saline and with incomplete and complete Freund's adjuvant are shown in Fig. 3. Immunofluorescence and immunoperoxidase tests showed that antilens antibodies belong to the IgG class. The possibility that they also belong to the IgM class, however, and also to other classes of immunoglobulins exists. Agar-gel diffusion, immunoelectrophoresis, and the Osserman test showed that extracts of iris, liver, and kidney from rabbits, guinea-pigs, and rats contained several antigenic substances which cross-reacted with antilens antibodies, mainly those against α-crystallins.

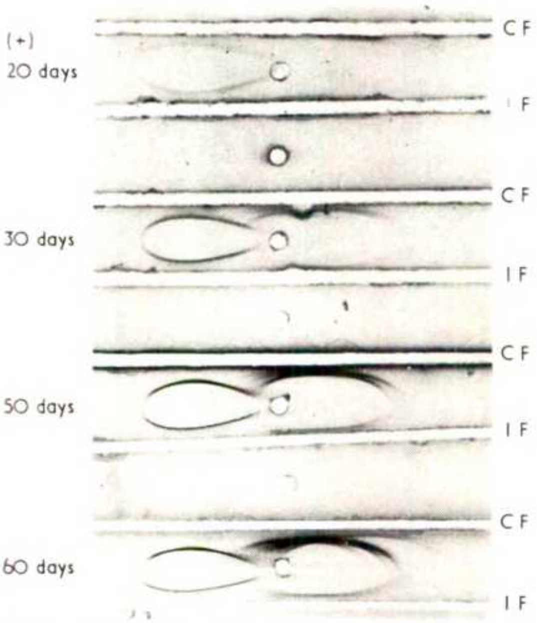

Fig. 2 *Agar-gel immunoelectrophoresis. The wells contain soluble lens proteins from a guinea-pig. The troughs are filled with heterologous lens antisera produced in rabbits with complete (CF) and incomplete (IF) Freund's adjuvant. Sera collected 20 days after immunisation contain antibodies to α-crystallins only. Although antibodies to β-crystallins are present on the 30th day of immunisation, antibodies to γ-crystallins are not even detectable 60 days after immunisation when the antigen was injected with Freund's incomplete adjuvant. They are present, however, when antigen and complete adjuvant are injected*

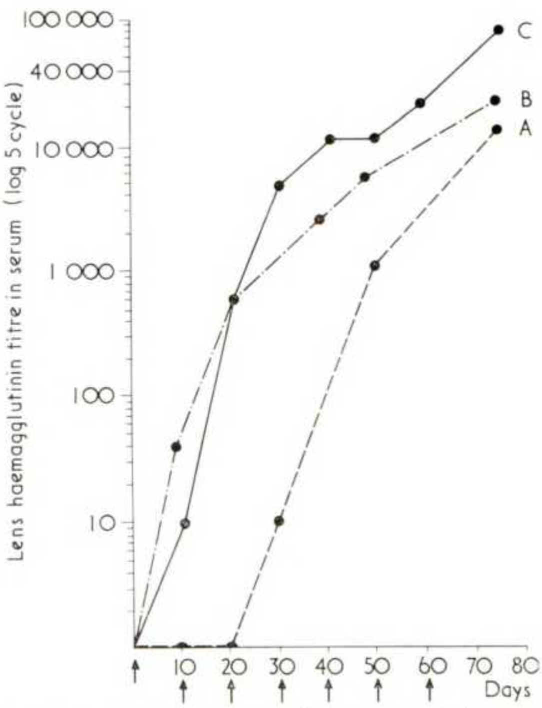

Fig. 3 *Kinetics of average antibody response in 3 groups of rabbits injected with heterologous lens in saline (A), in incomplete (B), and in complete (C) Freund's adjuvant. The arrows represent immunising injections*

The immunofluorescence test was positive with low-titre haemagglutinating sera, but the Ouchterlony test was found to be positive only when the haemagglutinin titre was 1:640 and more.

The immunofluorescence and immunoperoxidase tests showed that the antilens sera reacted strongly with the lens epithelium and the cortex. In addition, a positive reaction was seen with the iris, the ciliary body, the corneal epithelium, and the inner retina. Diffuse as well as coarse granular reactions were noted with gastric parietal cells and chief cells, hepatocytes, and renal tubular epithelium, suggesting the presence of antimitochondrial and antiribosomal antibodies in lens antisera. Moreover, some of the stronger antisera reacted with skeletal muscles in the rat diaphragm and smooth muscle fibres in the rat stomach and glomeruli, suggesting the presence of antibodies to contractile proteins. Some of the antisera also contained weak antinuclear antibodies (Figs. 4, 5, 6, 7, and 8).

The lymphocyte transformation test gave variable results. The transformation index was obtained by dividing the average radioactive count in the experimental tube by the average count in the control tube. The transformation index was highest (i.e., 2·5) when guinea-pig lens with Freund's adjuvant was used for immunisation. With incomplete adjuvant the index was only 1·5, whereas with saline homogenate very little change was observed. Animals immunised with complete and

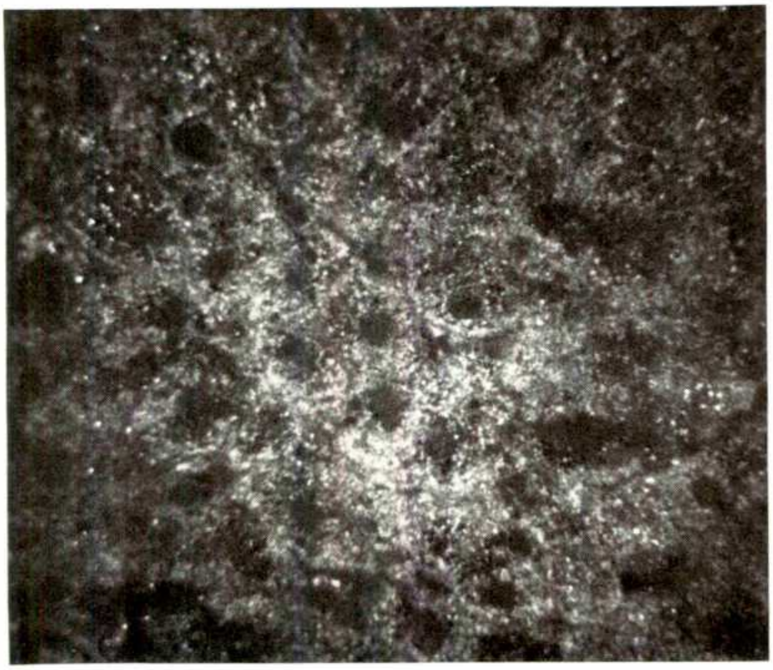

Fig. 4 *Indirect immunofluorescence test with unfixed sections of rat liver. The antilens serum reacts with cytoplasmic organelles (e.g., mitochondria and ribosomes) to produce a granular fluorescence.* ×*400*

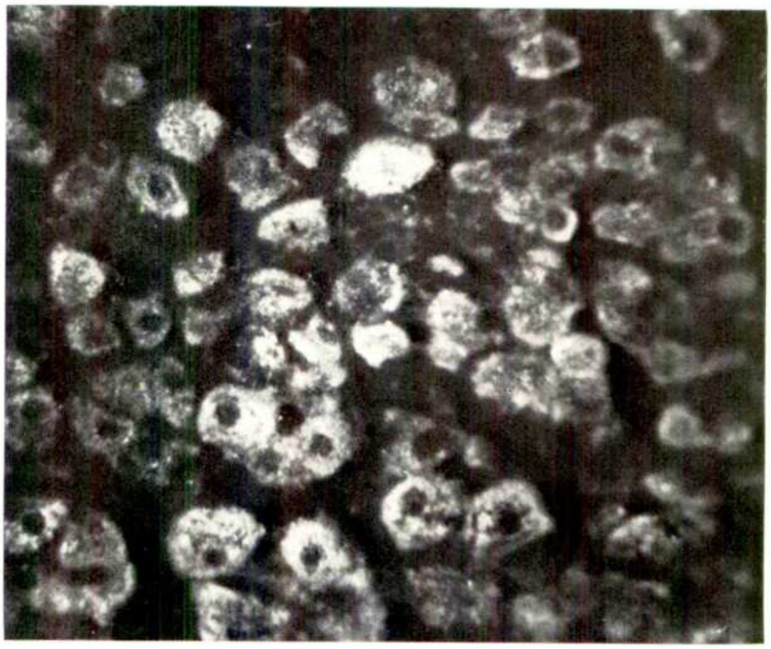

Fig. 5 *Parietal and chief cells of a mouse stomach, showing bright cytoplasmic fluorescence in the presence of lens antibody.* ×*315*

incomplete Freund's adjuvant but without lens protein showed no evidence of sensitisation to lens crystallins.

The changes in the skin in immunised rabbits after lens injection were minimal and showed a mixture of polymorphonuclear and lymphocytic infiltration. The needled eyes appeared inflamed clinically, as evidenced by circumcorneal congestion, aqueous flare, miosis, vasodilatation in the iris, and some cloudiness of the cornea, but the inflammation persisted for only a few days, and histological examination a week later showed little evidence of a typical phakoallergic endophthalmitis. The needled lenses showed only mild cellular infiltration, consisting mainly of macrophages, and the iris appeared haemorrhagic and congested; some inflammatory cells were present in the anterior chamber (Figs. 9 and 10).

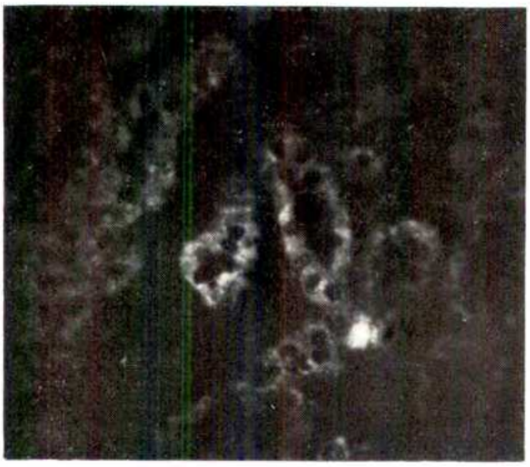

Fig. 6 *Lens antiserum containing antibodies to ribosomes. Note the patchy fluorescence of the renal tubules.* ×*285*

Discussion

The present study confirms earlier observations that soluble lens material consists of a large number of closely related but antigenically distinct components (Rao *et al.*, 1955; Manski, 1973) instead of only 4 proteins as previously suggested (Morner, 1894; Burky and Woods, 1928). It also confirms the findings of Manski *et al.* (1965) that heterologous immunisation as opposed to homologous immunisation leads to antibody production against the whole range of α-, β-, and γ-crystallins. We have shown for the first time, however, that the levels of both humoral and cellular immune responses to heterologous lens proteins injected with incomplete adjuvant are higher than with simple saline homogenates but much weaker than with complete adjuvant. This suggests that for a good antibody response, especially to low-molecular-weight lens proteins such as γ-crystallins, the presence of mycobacteria in the adjuvant mixture is essential. This is in contrast to the response to retinal antigens, in

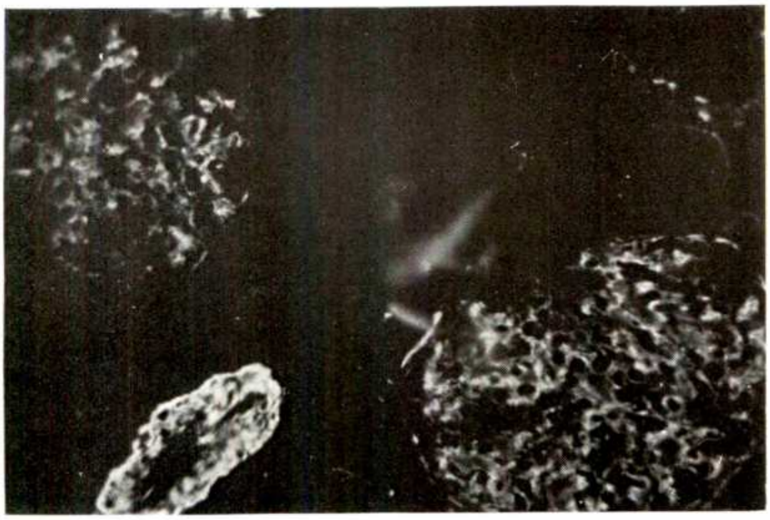

Fig. 7 *Positive indirect immunofluorescence test for antibodies to smooth muscle proteins. Two glomeruli and a blood vessel in a rat kidney show bright fluorescence.* × *380*

which mycobacteria may sometimes suppress the immune response (Wacker and Lipton, 1971). Furthermore, mycobacterial proteins, as evidenced by lymphocyte transformation studies, appear to be necessary also for an effective stimulation of T-lymphocytes, which are required not only for delayed hypersensitivity reactions but also for a good antibody response by B-lymphocytes through the well-known mechanism of cellular co-operation.

Although in most textbooks lens proteins are still considered to be sequestrated antigens, which means that animals should be intolerant to them and should be able to produce antibodies without the addition of adjuvant, our study showed that animals are in fact tolerant to at least γ-crystallins and that antibodies and cellular immune responses cannot be evoked without the use of an adjuvant enriched with mycobacterial proteins. Furthermore, the kinetics and the variability of the immune response studied in several groups of animals clearly shows the role of immunological tolerance. It is now known that the immune responsiveness to a variety of antigens is controlled by the immune response genes (i.e., Ir gene) which are associated with the major histocompatibility region of the chromosome (Ellman *et al.*, 1970). The present study clearly emphasises the role of mycobacteria and the immune response gene in humoral and cellular immunity to lens antigens in general and γ-crystallins in particular. It is known that γ-crystallins are of low molecular weight and that lens antigens are detectable in normal aqueous although in small amounts (Clayton *et al.*, 1968), so that it is possible that γ-crystallin acts in a similar way to serum thyroglobulin (Bankhurst *et al.*, 1973), leading to a state of immunological tolerance involving mainly the T-lymphocytes. This aspect of lens immunology has not been examined before and demands further critical study.

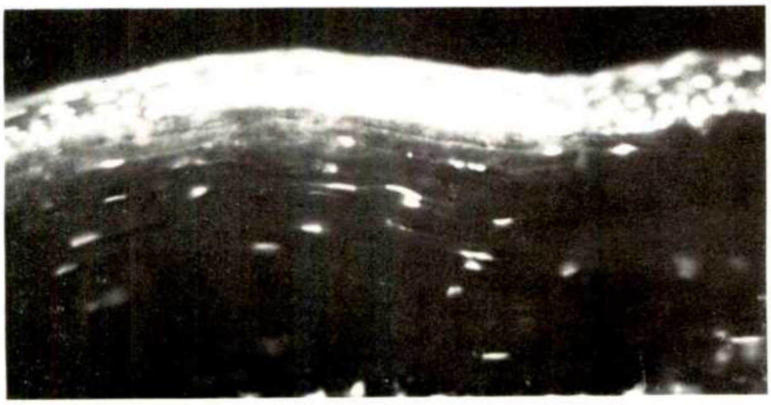

Fig. 8 *Hyperimmune serum from a rabbit injected with heterologous lens proteins in Freund's complete adjuvant. Antibodies react with the corneal epithelium and the keratocytes to produce nuclear fluorescence.* × *400*

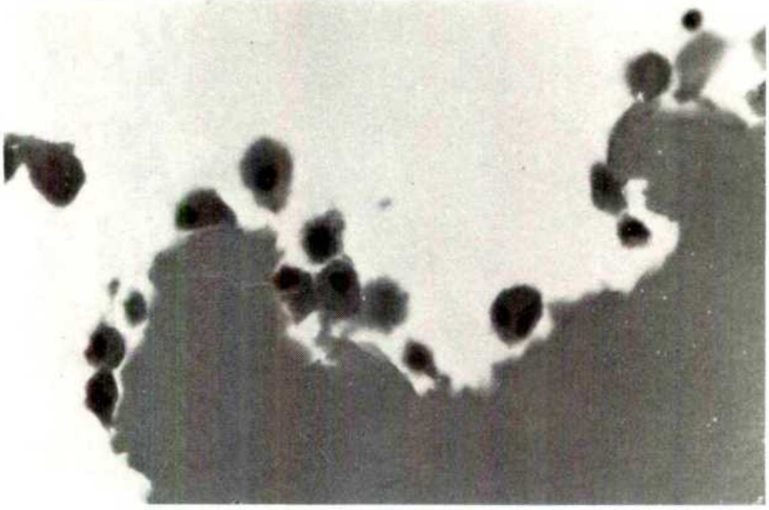

Fig. 9 *Phagocytic mononuclear cells surround the needled lens of an immune rabbit with circulating heterologous lens antibody. H and E. × 835*

A comparative study of the 5 different methods for the detection of specific antibodies which have been performed for the first time on the same serum samples shows clearly that the best method for detecting antibodies to lens proteins is the passive haemagglutination technique which becomes positive before the other tests. Immunofluorescence and immunoperoxidase tests are slightly less sensitive and perhaps more subjective. Agar diffusion and immunoelectrophoresis are least sensitive, being positive only when the lens haemagglutinin titres are 1:640 or more. The one advantage of the agar diffusion technique, however, lies in its capacity to detect and differentiate a large number of antigen-antibody systems in a heterogeneous mixture of proteins.

The immunofluorescence and immunoperoxidase tests have the one advantage over the haemagglutination and agar diffusion tests of being able to detect the chemical class of the immunoglobulins involved in an immune reaction. It has been possible, therefore, to state with certainty that IgG is involved in lens antibody reactions. This does not exclude, however, the role of other immunoglobulins.

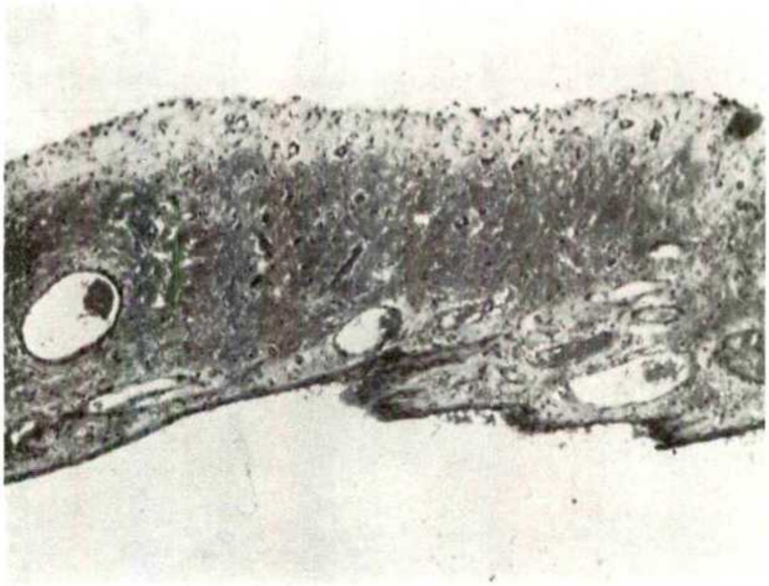

Fig. 10 *Mildly inflamed iris, showing mainly congestion and haemorrhage 1 week after discission of the lens in a rabbit immunised with heterologous lens in Freund's complete adjuvant. × 200*

Our study of cross-reactivity has shown for the first time that potent lens antisera contain antibodies to mitochondria, ribosomes, contractile proteins, and cell nuclei. As previously noted in this paper, lens epithelium and the superficial cortex contain all or most of these organelles, which are themselves complex structures made up of a variety of proteins both structural and enzymatic. Furthermore these organelles, though not discernible electron microscopically in the deeper regions of the lens (Hogan *et al.*, 1971), might be present as inspissated structureless masses. That this may be so is supported by the evidence that ribonucleoproteins (RNA) can be extracted in a large amount not only from the lens cortex but also from the lens nucleus (Maraini *et al.*, 1964).

By means of differential centrifugation and equilibrium centrifugation in density gradients it has been shown that antibodies which react with the chief cells of the stomach, the hepatocytes, and the renal tubular epithelium to give diffuse fluorescence are antiribosomal (antimicrosomal) antibodies, whereas those which react with gastric parietal cells, hepatocytes, and the tubular epithelium to give a rather granular fluorescence are antimitochondrial antibodies (Taylor *et al.*, 1962; Anderson *et al.*, 1967; Wright, 1975). It is of interest that both these antibodies are non-species and non-organ specific. It is now known that antibodies to contractile proteins such as myosin and actin, which are common in autoimmune disorders including uveitis, react well with smooth muscle fibres in the rat stomach, the blood vessels, and the glomeruli (Rahi *et al.*, 1976). A similar fluorescence observed with antilens sera clearly shows that these sera contain antibodies to cell mitochondria, smooth muscle contractile proteins, and ribosomes. The exact nature of the antigens associated with these organelles is unknown but it is possible that it is composed of a mixture of structural and enzymatic proteins. In this context it is of interest that microsomal fractions from non-mamallian species (e.g., chick liver) contain antigens resembling important soluble crystallin (FISC) and long-line crystallins (Vincentiis *et al.*, 1975) of the avian lens.

The modern concept that lens antigens, which were once believed to be organ-specific are neither tissue- nor species-specific (Perkins and Wood, 1963; Clayton *et al.*, 1968; Bours and Doorenmaalen, 1972) is compatible with the findings presented in this paper, which provide for the first time a rational explanation, at least in part, for the cross-reactivity of antilens sera. Almost every tissue in the body contains mitochondria, endoplasmic reticulum (i.e., the microsomes of the cell biochemist), nuclei, and contractile filaments and would be expected to cross-react with potent antisera produced against the lens homogenates, which for developmental reasons contain all these structures entrapped among the specific lens crystallins.

In our experiments systemic immunisation with heterologous lens protein followed by discission of the lens did not lead to a typical phakoallergic endophthalmitis. This is in keeping with the concept that heterologous antibodies are less pathogenetic than autoantibodies and that previous attempts to produce such inflammation resulted in variable and often unpredictable changes, and never typical granulomatous inflammation around the lens (Verhoeff and Lemoine, 1922; Burky, 1934; Scobee and Slaughter, 1944; Muller, 1952). It is known that the insoluble albuminoid is more potent than soluble lens crystallins in inducing T-cell sensitisation and therefore delayed tissue allergy (Manski, 1973). Since in the present study only soluble lens proteins were used, it is likely that the rabbits were not sufficiently sensitised to manifest a granulomatous reaction, which is the common histological feature of delayed hypersensitivity. That this is the case is supported by the fact that the animals in the present series did not show a marked lymphoblastic change when challenged *in vitro* with lens antigens. The histological changes in the needled eyes were reminiscent of a Schwartzman reaction.

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The role of axoplasmic transport in the pathogenesis of retinal cotton-wool spots

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SUMMARY Small retinal arterioles in the pig retina were occluded by argon laser photocoagulation and the morphology and topography of the resulting lesions studied by ophthalmoscopy, histology, and electron microscopy. Two days after laser coagulation ischaemic necrosis of the inner retina was observed in the territory of occluded arterioles, and swollen axon terminals packed with cytoplasmic organelles were found in the retinal nerve-fibre layer on the peripheral border of the infarcts and their border nearest to the disc. These swellings gave rise to localised zones of opacification (cotton-wool spots) at the borders of the retinal infarcts, and similar zones developed in relation to the laser burns.

Amino-acid uptake and transport in retinal ganglion cells was studied in these animals by autoradiography following an intravitreal injection of tritiated leucine. When ^{3}H-leucine was injected at the same time as laser coagulation and arteriolar occlusion, label became concentrated in the swollen axon-terminals on the peripheral aspect of 2-day-old infarcts but was absent from the terminals on the disc side of infarcts. The accumulation of ^{3}H-leucine and organelles was attributed to interruption of orthograde axoplasmic transport. When ^{3}H-leucine was injected into the vitreous 2 days prior to laser occlusion, label became distributed throughout the axoplasm and then accumulated in swollen axon terminals on both sides of infarcts after a further 2 days. An obstruction to both orthograde and retrograde axoplasmic flow was thus demonstrated.

We concluded that cotton-wool spots should be redefined as accumulations of cytoplasmic debris in the retinal nerve-fibre layer caused by obstruction of orthograde or retrograde axoplasmic transport in ganglion cell axons.

Cotton-wool spots are discrete opaque swellings of the inner retina found in a variety of systemic vascular disorders, including accelerated hypertension and diabetes mellitus. They consist of aggregates of 'cytoid bodies', which are the distended stumps of ganglion cell axons (Ashton and Harry, 1963), and their dense whiteness is thought to result from the light-scattering properties of cytoplasmic organelles concentrated within these terminals. Although cotton-wool spots are commonly considered to represent areas of focal retinal ischaemia, the histological and ophthalmoscopic characteristics of retinal infarction and cotton-wool spots are quite distinct. Ischaemic necrosis of ganglion-cell axons is not accompanied by organelle aggregation, and the inner retinal layers assume a grey translucent ophthalmoscopic appearance.

The first ultrastructural study of experimental focal ischaemia was carried out in the pig retina by Ashton *et al.* (1966). Within minutes of microsphere embolisation of the retinal circulation ischaemic cloudy swelling of nerve fibres developed in the territory of occluded arterioles, and as early as 5 hours after vascular occlusion organelles were found to have accumulated in axon terminals near the edge of the retinal infarcts. The aggregation of mitochondria, dense bodies, and other particles was attributed to a proliferative axonal response to hypoxia at the boundary of anoxic areas (Shakib and Ashton, 1966). However, it is known that organelles are normally synthesised only in the nerve cell body and are subsequently transported to and fro along axons between the synaptic terminals and the perikaryon (Jeffrey and Austin, 1973). This bi-

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directional movement of subcellular particles (and also molecules) is called 'axoplasmic transport', and interruption of this flow by axonal damage causes an accumulation of organelles in distended axon terminals adjacent to the injury site (Lubinska, 1964; Zelena, 1968; Banks *et al.*, 1969). This explanation for organelle aggregation in cotton-wool spots was discounted by Shakib and Ashton (1966) but can be reconciled with clinical findings in patients with retinal vascular occlusions (McLeod, 1975).

In an attempt to discriminate between these two potential sources of axoplasmic material in cotton-wool spots we studied amino-acid uptake and transport in ganglion cells of the pig retina by autoradiography following an intravitreal injection of tritiated leucine. Retinal infarcts were produced by laser coagulation of small retinal arterioles. Unlike microsphere embolisation of the retinal circulation, laser occlusion permitted an accurate prediction of the size and topography of the infarcts, and also allowed comparisons to be made between axonal changes occurring in ischaemic areas and those found in relation to the severe retinal damage caused by intense photocoagulation.

Material and methods

Four healthy white pigs aged between 6 and 12 weeks old were used in this study; they were fasted for up to 18 hours prior to each anaesthetic and received no premedication. Anaesthesia was induced by halothane and oxygen from a Boyle's machine via a snout mask, and maintained with halothane, nitrous oxide, and oxygen. The pigs were laid on their right sides, so the left eye was used in each experiment.

OPHTHALMOSCOPY, PHOTOGRAPHY, AND FLUORESCEIN ANGIOGRAPHY

The pupil was dilated with cyclopentolate eye-drops (0·5%) and phenylephrine eye-drops (10%), and the retina was observed by direct and indirect ophthalmoscopy; the position of the eye was controlled by means of stay sutures through the 4 rectus tendons. Particular attention was paid to the topography of the inner retinal circulation and the relationship between retinal arteriolar territories and the orientation of nerve fibre bundles.

Colour photographs and fluorescein angiograms were obtained using the vertically-mounted Zeiss (Oberkochen) fundus camera and processing methods previously detailed (Dollery *et al.*, 1966; Kohner *et al.*, 1970); 10% sodium fluorescein was injected into the external carotid artery via a nylon catheter introduced through an ear artery.

LASER PHOTOCOAGULATION

Laser light was delivered to the eye from an argon laser photocoagulator (Coherent Radiation model 800) using a vertically mounted and counterbalanced slit lamp and a Worst corneal contact lens. A segment of the arteriole selected for occlusion was repeatedly exposed to 0·2 s pulses of irradiation with a 50- or a 100-μm aperture and a power meter setting of 100 to 300 mW. Arterioles in the nasal retina were most conveniently irradiated, and occlusion was facilitated by intravenous injections of fluorescein. Further applications of laser light were made if there was any evidence of reopening of an arteriole.

INTRAVITREAL INJECTION OF ^{3}H-LEUCINE

One milliCurie of tritiated leucine (L-4,5^{3}H-leucine), specific activity 40 to 60,000 mCi/mmol (Radio-Chemical Centre, Amersham), was supplied dissolved in 1·0 ml of 2% ethanol, to which was added 0·009 g of sodium chloride. A limbal conjunctival incision was made superotemporally in the experimental eye of each pig and a small quantity of vitreous was aspirated via a sclerotomy over the pars plana. 0·33 ml of ^{3}H-leucine was then injected into the posterior vitreous while the tip of the needle was observed by indirect ophthalmoscopy; the sclera and conjunctiva were then sutured. In pig No. 4 the initial vitreous aspiration proved difficult, and an anterior chamber paracentesis was performed after intravitreal injection of label in order to restore a normal intraocular pressure.

SEQUENCE (TABLE 1)

In pigs Nos. 1 and 2 ^{3}H-leucine was injected immediately after arteriolar occlusion, that is, at about one hour from the onset of retinal ischaemia (experiment A). In pigs Nos. 3 and 4 ^{3}H-leucine was injected into the vitreous 2 days prior to arteriolar occlusion (experiment B). In all four animals the ischaemic lesion was allowed to develop for 48 hours before enucleation; the animals were then killed by intravenous injections of potassium chloride solution.

MICROSCOPY

Immediately after enucleation, a coronal incision was made in the cornea, and the eyes were immersed

Table 1

Day	*Experiment A* *(Pigs No. 1 and 2)*	*Experiment B* *(Pigs No. 3 and 4)*
1	Arteriolar occlusion + intravitreal ^{3}H-leucine	Intravitreal ^{3}H-leucine
3	Enucleation	Arteriolar occlusion
5	—	Enucleation

in 100 ml of fixative. Initial fixation was achieved by 3% glutaraldehyde buffered in 0·1 M sodium cacodylate containing 10 mg/ml calcium chloride and with a final pH of 7·4. The eyes were progressively dissected in this solution and the anterior segments, together with the lens and vitreous, were discarded. After a total fixation time of 45 minutes a detailed drawing was made of the fundus, recording the topography of both the laser lesions and the ischaemic areas. Experimental areas were then isolated by microdissection under a dissecting microscope. Each sample was incised in such a fashion that its orientation with regard to the optic disc could be determined during ultramicrotomy. Samples were then briefly washed in 0·1 M sodium cacodylate buffer containing 7·5% sucroses; they were then dehydrated through a graded series of concentrations of ethanol in water and embedded in Epon via epoxypropane. Subsequent procedures for light and electron microscopy were identical to those previously described (Marshall, 1970). In every sample sections were cut both parallel with and at right-angles to the axons of retinal ganglion cells.

LIGHT MICROSCOPIC AUTORADIOGRAPHY

Sections approximately 0·8 μm thick were cut using glass knives in a Cambridge Huxley Mk 1 ultramicrotome and were mounted on freshly cleaned unsubbed glass slides. All subsequent handling procedures were carried out under a brown safe light (Ilford S902). Slides were coated with a nuclear emulsion (Ilford K5) using an automatic coating device (Marshall and Faulkner, 1977); they were dried horizontally for 15 minutes and then hung vertically over silica gel for 2 hours in a light-tight box. The dried coated slides were placed in small light-tight plastic boxes containing silica gel and stored at 4°C for 1 week. They were then developed and stained as previously described (Marshall and Voaden, 1974).

The majority of slides in this study had grain concentrations over the nerve-fibre layer of such magnitude that microscopic counting was tedious and confusing. To facilitate evaluation of the large number of sections involved, and to reduce sampling errors, slides were scanned in a Shimadzu spectrophotometer (MPS 50L) fitted with a microspectrophotometry attachment. The monitoring beam was adjusted to a size (20 μm square) such that only signals from the nerve-fibre layer were measured; changes in optical density due to the background stain (toluidene blue) were minimised by carrying out all measurements in a blue light (550 nm, 10 nm half band width). Sample areas and the precise position of the monitoring beam were recorded photographically for each location on the slide. Results were plotted as changes in optical density due to the concentration of grains against their location in the retinal nerve-fibre layer (Fig. 9). Grain counts from some of the less dense slides showed this method to be linear. Thus after calibration density plots could be converted into grain counts.

ELECTRON MICROSCOPIC AUTORADIOGRAPHY

Sections for electron microscopic autoradiography were cut on diamond knives mounted in an OMU3 Reichert ultramicrotome. Subsequent procedures were identical to those previously described (Bok and Young, 1972) except that L4 (Ilford) emulsion diluted 1 : 5 was applied to the slides using the automatic coater. All slides were exposed for 4 weeks.

The large contrast range of EM6 (Ilford) photographic plates enabled the autoradiographic grains to be readily discriminated, but identification became more difficult when such plates were printed owing to the reduced contrast range of photographic papers. To avoid confusion between grains in the nuclear emulsion and organelles of similar size and density on photographic prints a masking technique was employed. Negatives of electron microscopic autoradiographs were printed on to Kodalith (Type 3 Estar 2556) film at the same size as the final print and with an exposure such that only the autoradiographic grains gave rise to an image. The film was then developed, dried, and placed on top of the paper for the final print, but slightly offset. A second exposure was made and the paper developed and fixed in the normal way. The resulting prints had a black spot from the negative reversal process and a white edge due to the mask.

Results

OPHTHALMOSCOPY AND FLUORESCEIN ANGIOGRAPHY

No pre-existing funduscopic abnormalities were noted in any of the eyes, and uniform filling of the retinal capillary bed by fluorescein was demonstrated prior to vascular occlusion. Slight haziness of the vitreous tended to obscure the fundus view after the intravitreal injection of ^{3}H-leucine.

Laser coagulation of arterioles resulted in an immediate localised opacification of irradiated tissue, with obstruction to the passage of fluorescein dye along the arterioles and narrowing, darkening, and segmentation of the blood column distal to the site of occlusion. Within 2 hours of laser irradiation the inner retina in the territory of occluded vessels became swollen, highlighting the interwoven course of nerve-fibre bundles in the inner retina (Fig. 1*a*). The distribution of ischaemic swelling corresponded to the area of non-filling noted during the fluorescein

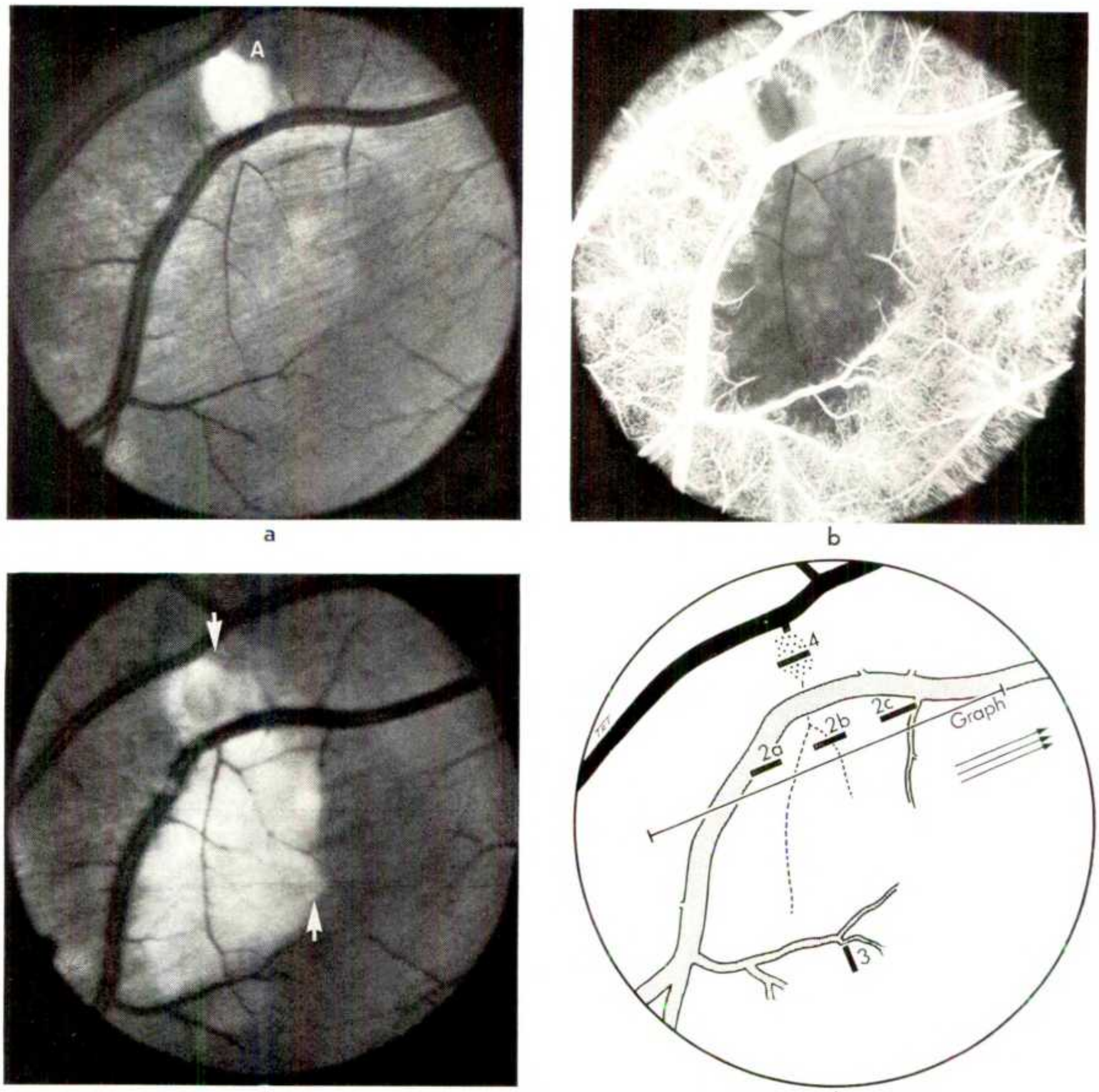

Fig. 1 *(a), (b), (c), and (d) Nasal retina of pig No. 1.* (a) *Fundus photograph from colour transparency 2 hours after arteriolar occlusion.* A *is the arteriole occluded by laser photocoagulation.* (b) *Fluorescein angiogram 2 hours after arteriolar occlusion: early arteriovenous phase.* (c) *Fundus photograph from colour transparency 2 days after arteriolar occlusion. Zones of dense opacification on the disc side of the laser lesion and the infarct are arrowed.* (d) *Key diagram of laser lesion and ischaemic area. The orientation of nerve-fibre bundles is arrowed, and the arrows point towards the optic disc. The figure numbers of light microscopic sections are shown, and 'graph' refers to Fig. 9*

angiographic transit (Fig. 1*b*). The surrounding retina was perfused normally, and there was gradual capillary in-filling at the periphery of ischaemic areas. No leakage of fluorescein was noted within the infarcts, but dye leaked profusely from the laser burns.

Two days after arteriolar occlusion both the laser lesions and the retinal infarcts had changed in their appearance. The central parts of laser lesions were now less opaque and localised zones of white retinal swelling were seen on either side of the irradiated areas, particularly on the disc-side of the lesions.

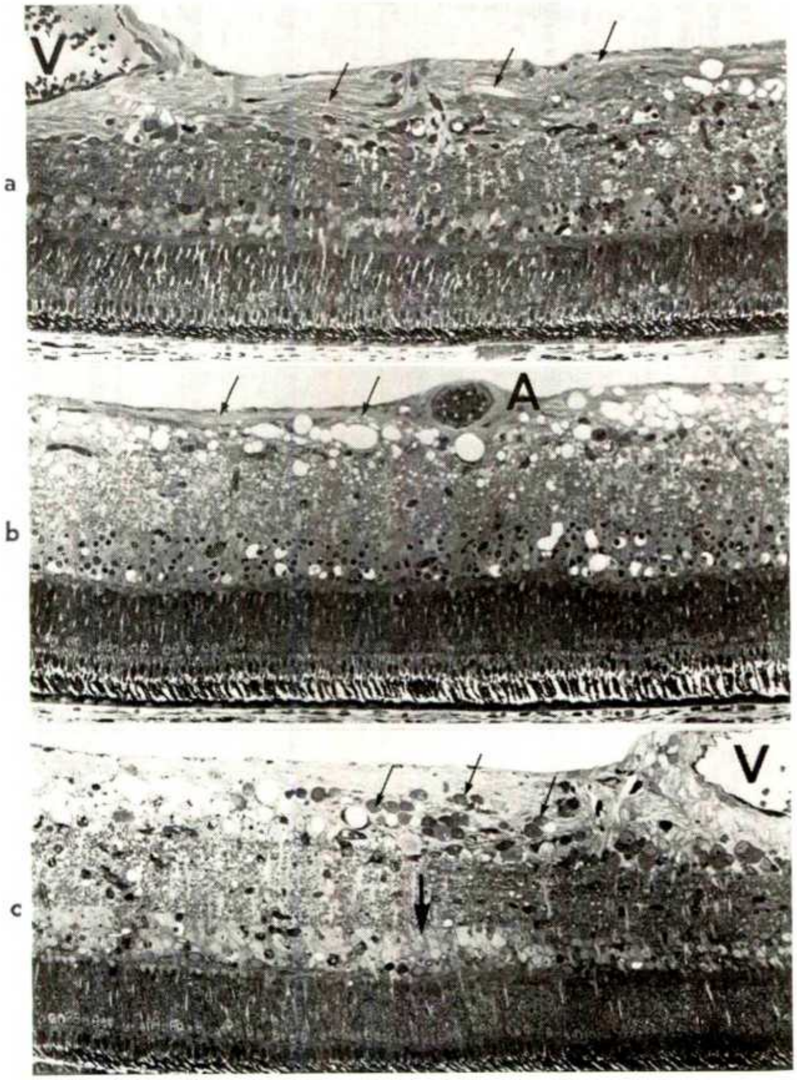

Fig. 2 *(a), (b), and (c)* *Light micrographs of the 3 distinctive zones associated with the ischaemic area illustrated in Fig. 1; all sections were cut along the axis of ganglion-cell axons.*

(a) *Zone PZ: An area characterised by abnormally swollen axons (fine arrows) in the nerve-fibre layer at the peripheral edge of the ischaemic area.* V *vein shown in Fig. 1.*

(b) *Zone IZ: The central part of the ischaemic area including the occluded arteriole* A. *The nerve-fibre layer is vacuolated, and anoxic damage extends through the inner plexiform layer to the inner nuclear layer where the nuclei are pyknotic. Some nerve fibres of normal appearance are seen near the inner limiting membrane (fine arrows). The outer retinal layers appear relatively normal throughout the section.*

(c) *Zone DZ: The border zone on the disc side of the ischaemic area; it is characterised by spheroidal axon swellings in the nerve-fibre layer (fine arrows). The coarse arrow marks the limit of ischaemic changes in the deeper layers of the inner retina;* V *is a vein seen in Fig. 1.* × *180*

The ischaemic inner retina had become more translucent and swollen than at 2 hours, and the nerve fibre bundle striation could no longer be readily defined. Furthermore, a zone of denser opacification had developed in the nerve-fibre layer where nerve fibres crossed the borders of ischaemic areas. Again, this swelling was most noticeable on the disc side of infarcts (Fig. 1*c*), especially in the peripapillary region, where the nerve-fibre layer was thickest. The infarcts remained poorly perfused by dye on fluorescein angiography.

LIGHT MICROSCOPY

In the territory of occluded arterioles changes were seen in all layers of the inner retina while the receptor cells and pigment epithelium remained undamaged; only abnormalities in the nerve-fibre layer will be described in detail. Pathological changes in ganglion-cell axons occurred in three zones which merged into each other: (i) a zone at the peripheral edge of the ischaemic area away from the optic disc (PZ), (ii) an intermediate zone (IZ), and (iii) a zone at the edge of the ischaemic area adjacent to the disc (DZ). The extent of these regions varied between individual lesions, but they were always sufficiently distinct to be recognised morphologically. Representative examples of these zones are shown in sections cut parallel to the axis of ganglion-cell axons (Fig. 1*d*; Fig. 2*a, b, c*).

Most ganglion-cell axons become swollen near

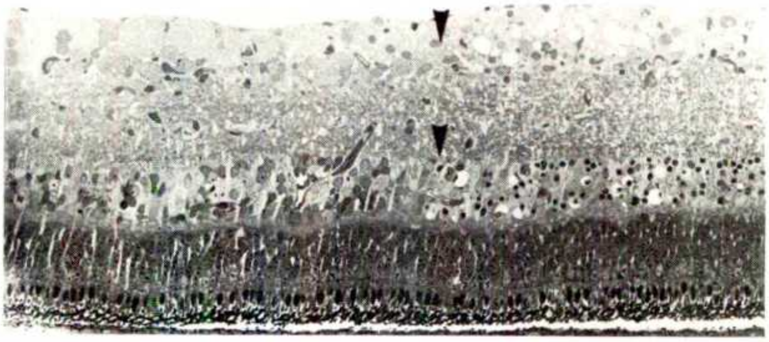

Fig. 3 *Light micrograph of the edge of the ischaemic area illustrated in Fig. 1; the plane of this section is at right-angles to the long axis of ganglion-cell axons. There is a sharp transition (arrowed) between normal tissue and ischaemic retina characterised by vacuolation in the nerve-fibre layer and nuclear pyknosis in the inner nuclear layer. There is no transitional zone of axonal swelling in the nerve-fibre layer.* × *180*

the peripheral edge of an ischaemic area, producing the region PZ. However, this was a relatively diffuse region, and axons often penetrated some way into this area before significant swelling was seen. There was a more abrupt transition between normal and ischaemic tissue in the ganglion cell and deeper layers of the inner retina, where shrunken pyknotic nuclei could be seen (Fig. 2*a*).

In the intermediate region (IZ) the nerve-fibre layer was extremely vacuolated and contained fewer axons than equivalent non-ischaemic retina (Fig. 2*b*). This loss of fibres was seen most clearly in sections from the edge of the lesion cut at right-angles to the long axis of the axons (Fig. 3), and a majority of those axons remaining within IZ were either shrunken or swollen. In most lesions the least affected axons were concentrated on the vitreal aspect of the nerve-fibre layer.

The border zone DZ (on the disc side of a retinal infarct) was more circumscribed than that on the peripheral aspect of the infarct. In this zone, large spheroidal axon swellings (sometimes designated 'cytoid bodies') were observed where axons emerged from the area of ischaemia, which was defined by another relatively abrupt transition from necrotic to normal tissue in the layers of the inner retina deep to the nerve-fibre layer (Fig. 2*c*).

Pathological changes in axon segments adjacent to laser burns were identical to those seen at the borders of retinal infarcts despite the different mechanism of axonal interruption. Differences in axonal responses in region PZ compared with DZ were readily demonstrable, since these zones were closer together in the laser lesions (Fig. 4).

ELECTRON MICROSCOPY

Retinal ganglion-cell axons varied in cross-sectional diameter between 0·25 and 1·50 μm in control areas of pig retina. Peripheral to the edge of an ischaemic area some swollen axons (3 to 5 μm diameter) were observed containing abnormal concentrations of neurofilaments. Within PZ many axons terminated in swellings of 3 to 10 μm diameter and contained abnormally dense concentrations of organelles. Typically, the neurotubular array within these axons was disorganised, and neurofilaments were concentrated in the centre of axons with many small mitochondria lining the axolemma (Fig. 5*a*). However, in the largest axons this arrangement was lost and the mitochondria and vesicular inclusions became distributed throughout the axoplasm. The swellings sometimes contained dense inclusions, some of which appeared to be lysosomes, while others were larger and resembled the lipid bodies that are associated with the breakdown of membrane systems.

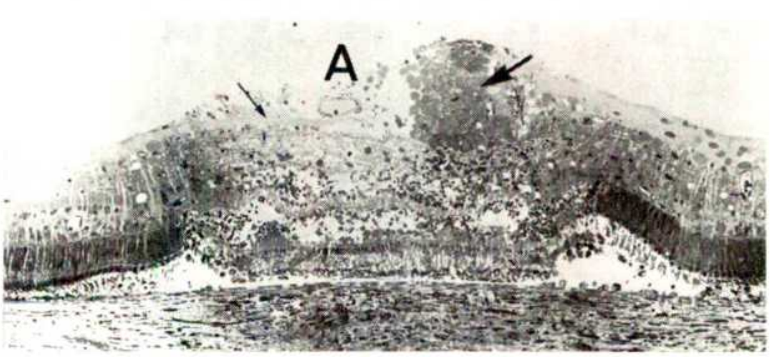

Fig. 4 *Light micrograph of the laser irradiated area which resulted in occlusion of the arteriole* A *illustrated in Fig. 1. A zone of axonal swelling is seen on the peripheral aspect of the lesion (fine arrow), and globular axon swellings are present on the disc side of the lesion (coarse arrow). Within the irradiated zone the nerve-fibre layer is destroyed together with the inner limiting membrane.* × *180*

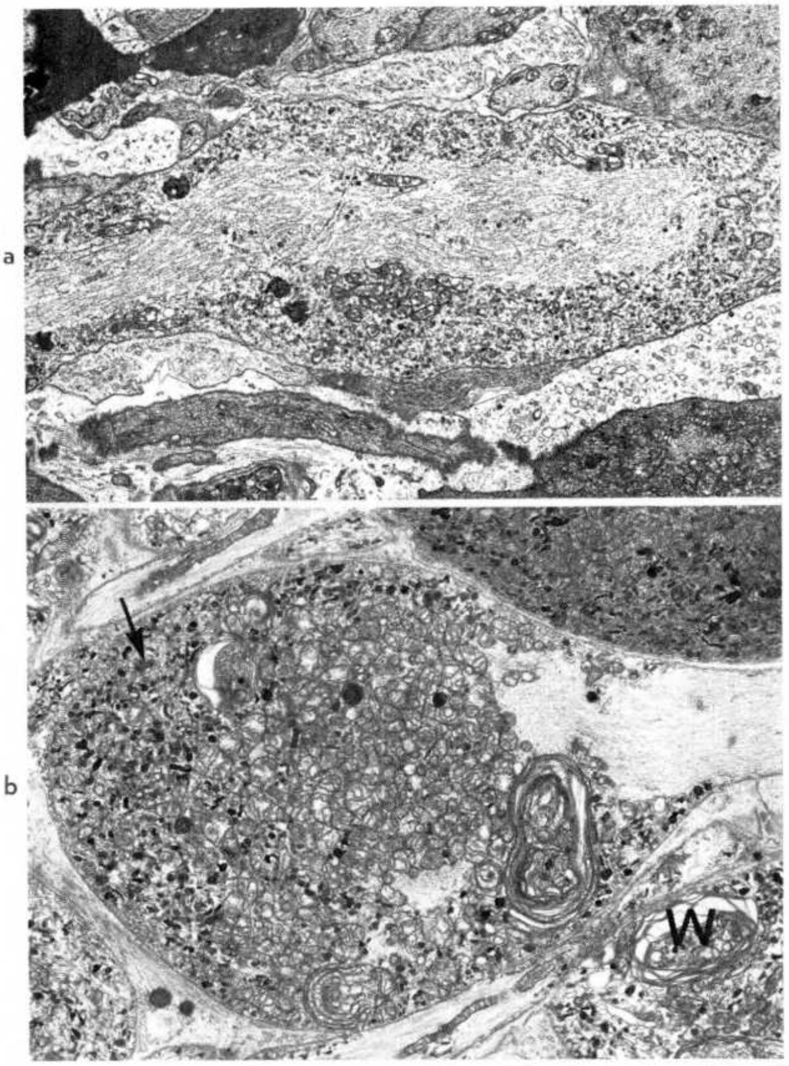

Fig 5 *(a) and (b) Electron micrographs of axonal swellings in zones PZ and DZ adjacent to the ischaemic area illustrated in Fig. 1.*

(a) *Axons in PZ are characterised by an elongated swelling with an aggregation of neurofilaments centrally and an accumulation of mitochondria and other organelles adjacent to the axolemma.*

(b) *Axon terminals in DZ are globular and contain dense concentrations of mitochondria, many of which are shrunken and degenerate (arrow), together with membranous whorls* W. × *6300*

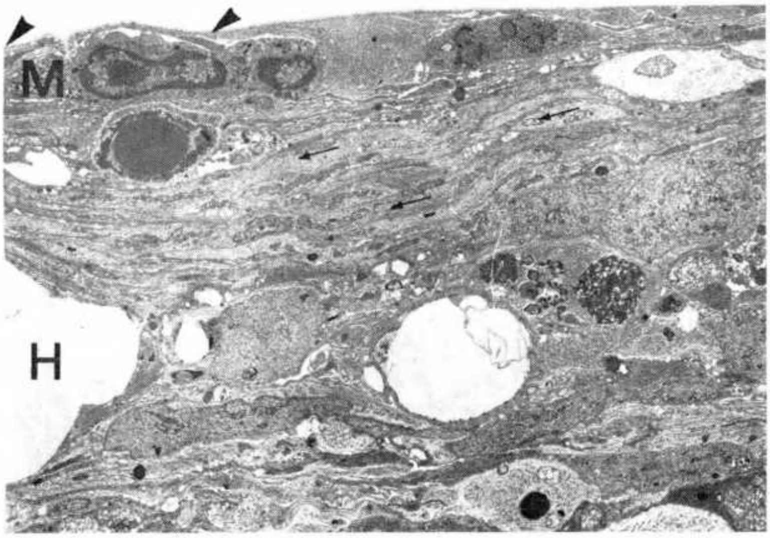

Fig. 6 *Electron micrograph of the nerve-fibre layer within the central zone (IZ) of the ischaemic area illustrated in Fig. 1. Degenerative processes affecting axons include vacuolation* H *and intra-axonal densification. Axons of relatively normal appearance (fine arrows) are seen beneath the inner limiting membrane (coarse arrows) together with macrophages* M. × *3400*

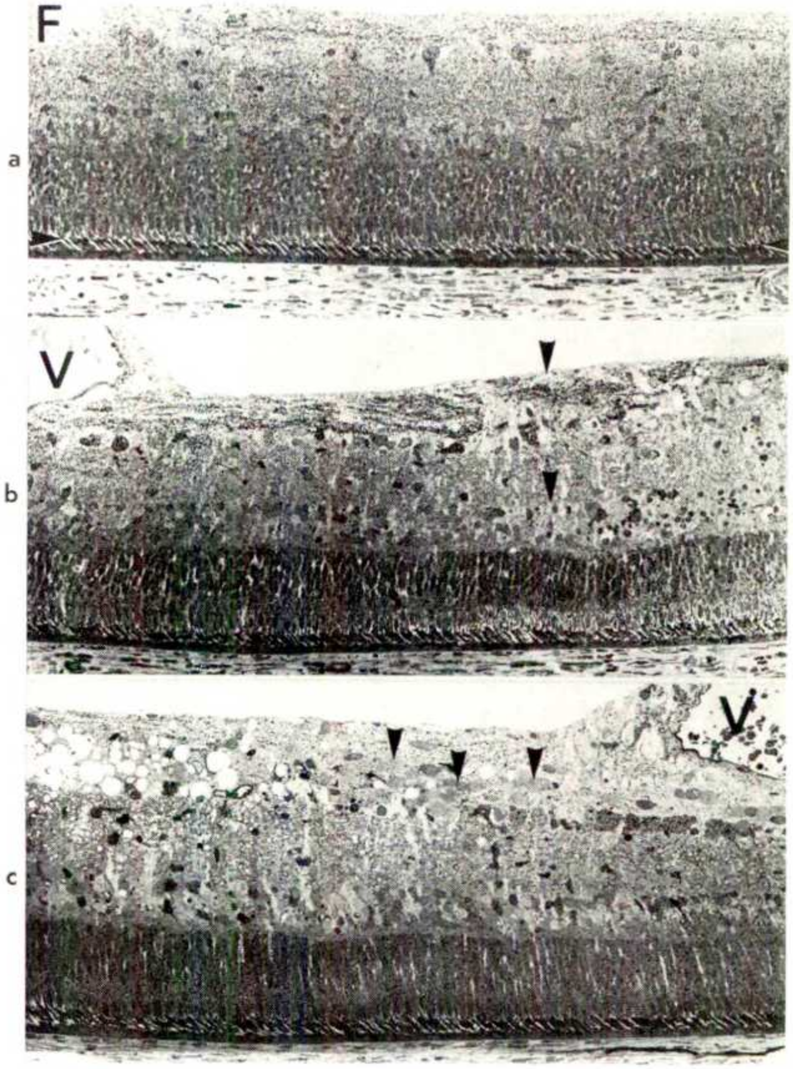

Fig. 7 *(a), (b), and (c) Light microscopic autoradiographs of ^{3}H-leucine incorporated into the retina of pig No. 1 (experiment A); sections were cut along the axis of ganglion-cell axons.*

(a) *A control area showing ^{3}H-leucine uptake into the retina, with high concentrations of label over the nerve-fibre layer* F *and over the ciliary regions of photoreceptor outer segments (arrowed).*

(b) *Autoradiograph showing ^{3}H-leucine distribution at the peripheral edge (arrowed) of the ischaemic area. An extremely high concentration of label is associated with the area of axonal swelling (PZ).* V *is a vein in Fig. 1.*

(c) *Autoradiograph showing ^{3}H-leucine distribution in zone DZ. Grains are absent over the spheroidal axon swellings in this region (arrowed). The grains over the innermost part of the nerve-fibre layer reflect the presence of surviving axons beneath the inner limiting membrane.* V *is a vein in Fig. 1. ×180*

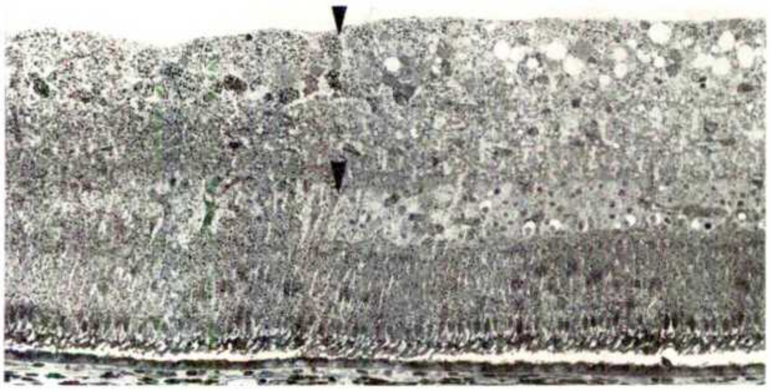

Fig. 8 *Light microscopic autoradiograph through the edge (arrowed) of the area of ischaemia in Fig. 1; the plane of section is at right-angles to the axis of ganglion-cell axons. No grains are seen over vacuolated or densely staining axons within the ischaemic area, but there are comparable grain densities over axons outside this area and surviving axons beneath the inner limiting membrane within the area of ischaemia. ×180*

Within the intermediate zone (IZ) extreme axonal damage was seen. Many axons were devoid of organelles and remained only as membrane-bound vacuoles, while others contained an amorphous remnant of the axoplasm together with shrunken or swollen mitochondria. In some areas the membranes bounding the axon ghosts had burst and irregular vacuoles were formed that extended over large areas of the nerve-fibre layer. Alternatively, some of the damaged fibres were shrunken and so electron-dense that no substructure could be determined. However, apparently normal axons were also identified among damaged axons in the inner part of the nerve-fibre layer.

The spheroidal axonal swellings seen in region DZ measured 10 to 15 μm in diameter and contained vast numbers of either shrunken or swollen mitochondria. Large numbers of neurofilaments were usually seen adjacent to this concentration of mitochondria in the part of the axon running away from the lesion towards the optic disc, but few if any neurotubules were observed. Many terminals contained the electron-dense lipid bodies previously described, and almost all contained membranous whorls which characterise degenerating membrane systems (Fig. 5*b*).

Macrophages were observed throughout the ischaemic area but were most abundant around capillaries and within the abnormally distended extracellular space beneath the inner limiting membrane; a large number of these cells contained accumulations of lipid globules (Fig. 6). The Müller's fibres appeared relatively normal, but some contained lipid globules and other membranous whorls.

The ultrastructural changes in the nerve-fibre layer in relation to laser lesions were similar to those described above. Areas PZ and DZ were more discrete, however, and the central region contained few if any normal fibres. Indeed, the majority of axons in this irradiated zone IZ were unrecognisable, while the remnants were either granular aggregations of coagulated protein or membrane-bound vacuoles.

AUTORADIOGRAPHY

Two distinct patterns of grain distribution could be observed in the nerve-fibre layer in relation to ischaemic areas, the distinction depending on the time at which ^{3}H-leucine was injected into the animals. Uptake into the outer retinal layers was similar in all experiments and identical to that of control tissue (Fig. 7*a*).

Experiment A

Dense localised accumulations of grains were found at the peripheral edge of ischaemic areas, with tracts of grains clearly visible traversing PZ and penetrating various distances towards the central zone IZ before terminating in a bulb-like distribution of extremely high grain density (Fig. 7*b*). A relatively high grain distribution was also observed over the nerve-fibre layer peripheral to PZ when compared with control tissue. This increase in grain density became less marked with increasing distance peripherally from PZ. The axon terminals in DZ were always devoid of grains, and this lack of grains extended for some distance along the nerve-fibre layer towards the optic disc (Fig. 7*c*).

A reduced grain count was found in IZ when compared with control tissues and any high localised counts were always associated with tracts of surviving axons extending from PZ. In addition, a few grains were found beneath the inner limiting membrane throughout the ischaemic area. The relatively low grain count in IZ was best demonstrated in sections taken from the edge of the lesion and cut at right-angles to the long axis of the axons (Fig. 8).

These observations were verified and quantified by scanning the sections in the spectrophotometer. A typical example of axonal grain distribution in relation to an ischaemic area is shown in Fig. 9.

Electron microscopical autoradiographic preparations further clarified the grain distribution described

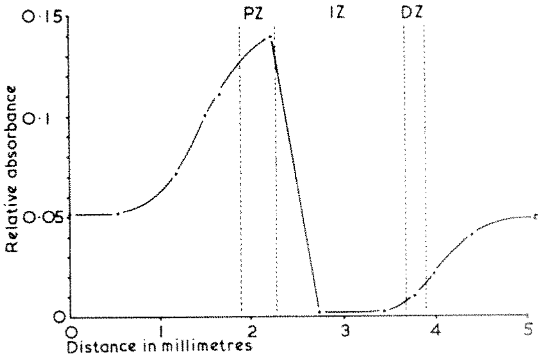

Fig. 9 *Graph showing variation in relative absorbance (optical density) in the nerve-fibre layer with position in the retina as measured on a spectrophotometer. This is a typical trace and derives from sections taken along the line marked in Fig. 1 (d). The base line was set on the lowest density sample, and a suitable range selected to give a full scale deflection in the densest areas. The relative absorbance gives a measure of variation in grain density throughout the specimen. PZ = zone of proximal axon terminals at the peripheral edge of the ischaemic area. IZ = intermediate zone of inner retinal infarction. DZ = zone of distal axon terminals on the disc side of the ischaemic area*

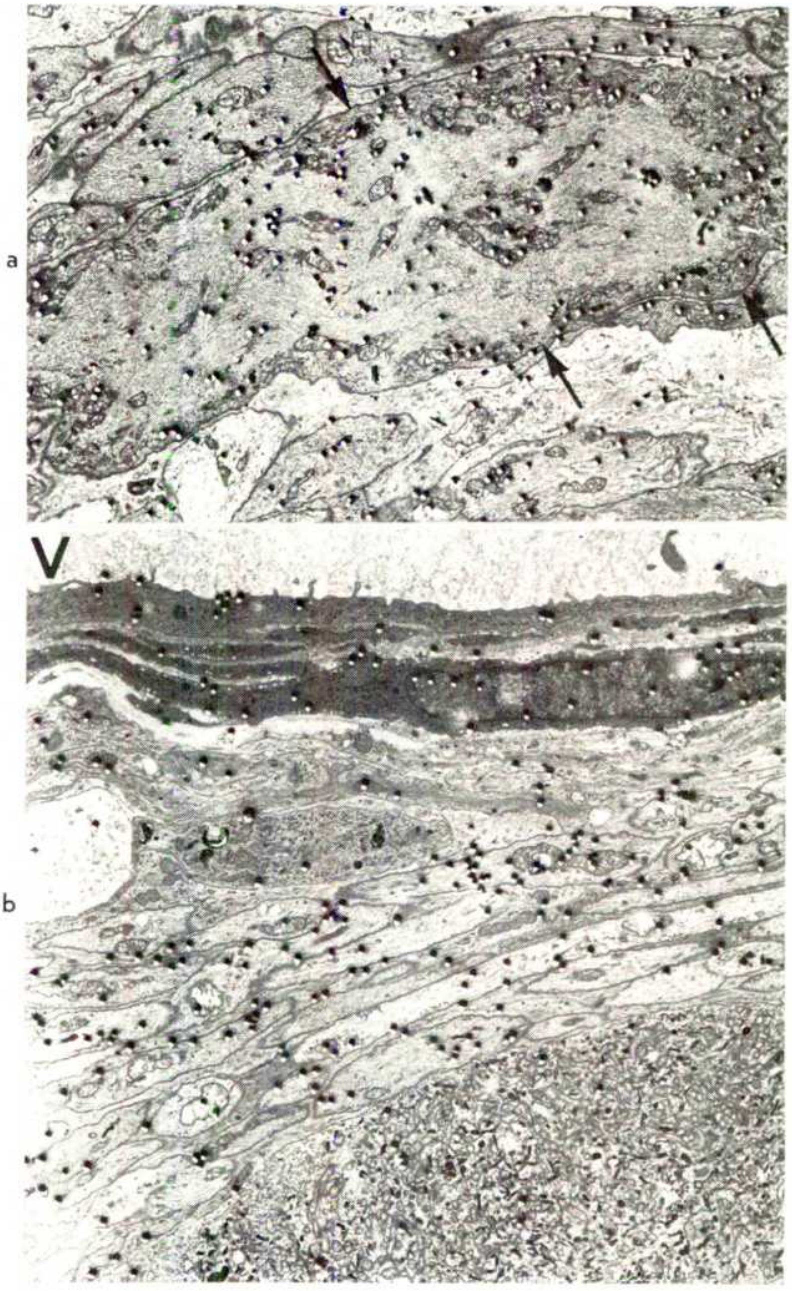

Fig. 10 *(a) and (b) Electron microscopic autoradiographs showing the distribution of* ^{3}*H-leucine in an axon terminal from PZ compared with that in a spheroidal terminal from DZ in experiment A (pig No. 1). Tonal contrasts in grains were achieved by a masking technique (see methods).*

(a) *A dense accumulation of grains is characteristic of swollen axons in PZ, and most of this label is associated with the organelles juxtaposed to the axolemma (arrowed).*

(b) *The spheroidal axon terminal from DZ is virtually free of grains as in Fig. 7 (c). Occasional grains seen over the distal axon terminal are not significant when background and resolution are taken into account.* V *is the lumen of the vein in Fig. 1.* ×*5580*

above. Grains were associated with both glial and axonal components of the nerve-fibre layer in the control areas of retina. In region PZ high grain densities were observed over the areas of axonal swelling and mitochondrial aggregation (Fig. 10*a*). No grains were found over areas of vacuolation in IZ (given the resolution of this technique (Salpeter *et al.*, 1969; Gupta *et al.*, 1973)), and grains were again absent over the spheroidal axon terminals in region DZ (Fig. 10*b*).

Experiment B

By light microscopical autoradiography a similar though less dense grain accumulation was found in region PZ when compared with experiment A. In these sections tracts were also observed extending towards IZ, but the contrast of grain density was reduced because of the increase in the general grain density in IZ. The axon terminals in zone DZ were also associated with relatively dense localisations of autoradiographic grains (Fig. 11), and increased grain densities could be seen extending away from both PZ and DZ. Electron microscopic autoradiographic preparations of tissue from B-type experiments confirmed the above observations; grains were clearly seen associated with the distal axon terminals in area DZ (Fig. 12).

The differences in grain distribution in experiment A compared with experiment B were also clearly demonstrable in autoradiographs from laser lesions, where the zones PZ and DZ were in closer proximity (Fig. 13).

Discussion

Swollen axon terminals develop on either side of injuries to myelinated and unmyelinated nerve fibres of both the peripheral and central nervous systems (Perroncito, 1907; Ramon Y Cajal, 1928). In the nerve-fibre layer of the retina terminal swellings have been described on either side of axonal interruptions caused by intense photocoagulation or sectioning, and appear to be responsible for localised opaque swelling of an otherwise transparent inner retina (Okun and Collins, 1962; Wolter and Moorman, 1966; Goldberg and Galin, 1973). In our study swollen terminals were also found on both sides of axon segments damaged by ischaemia, which is in keeping with the clinical topographical observation that localised zones of white swelling develop on both the peripheral and disc-adjacent borders of grey retinal infarcts after retinal vascular occlusions (McLeod, 1975). The ophthalmoscopic delineation of these border zones was sometimes difficult in our experiment owing to the thinness of the nerve-fibre layer of the nasal retina of pigs, but these zones were clearly defined histologically. Our findings are at variance with the view that only swollen axon terminals on the cell body side of ischaemic axon segments are important in the pathogenesis of retinal cotton-wool spots (Wolter, 1959; Shakib and Ashton, 1966; Ashton, 1970).

PATHOGENESIS OF AXONAL SWELLING

The development of terminal swellings on the stumps of interrupted axons suggested to Cajal a 'regenerative phase of survival of axons before the final withering' (Ramon Y Cajal, 1928). The axon swellings have subsequently been shown to contain aggregations of those organelles which are normally distributed along the length of the axon, together with an accumulation of proteins including enzymes (Lubinska, 1964). Quantitative studies and double-ligation experiments indicate that the enzymes concentrated in axon terminals, including some localised within mitochondria, are derived from uninjured parts of the axons, and are not synthesised locally (Lubinska, 1964; Banks *et al*, 1969). Their accumulation has been attributed to a damming-up of the normal bidirectional flow of axoplasmic constituents along axons, which necessarily requires that axoplasmic flow continues for some time after axonal section—Cajal's 'agony of the axons'. Interruption of orthograde axoplasmic transport results in an accumulation of axonal material on the proximal side of an injury, while obstruction to retrograde transport gives rise to a distal accumulation; similar accumulations occur whatever the type of axonal injury whether traumatic, thermal, toxic, or anoxic.

Axoplasmic transport in retinal ganglion cells has the same essential characteristics as in other nerve

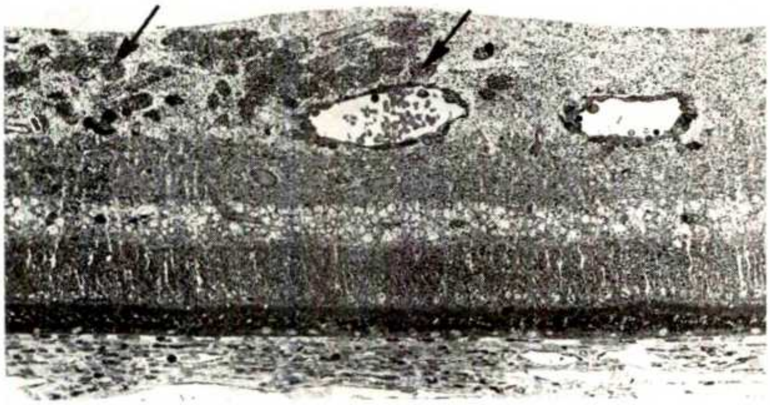

Fig. 11 *Light microscopic autoradiograph showing the zone DZ of the ischaemic area in pig No. 3 (experiment B); the section was cut along the axis of ganglion-cell axons. The spheroidal axon terminals (arrowed) are associated with a high concentration of* ^{3}*H-leucine.* × *180*

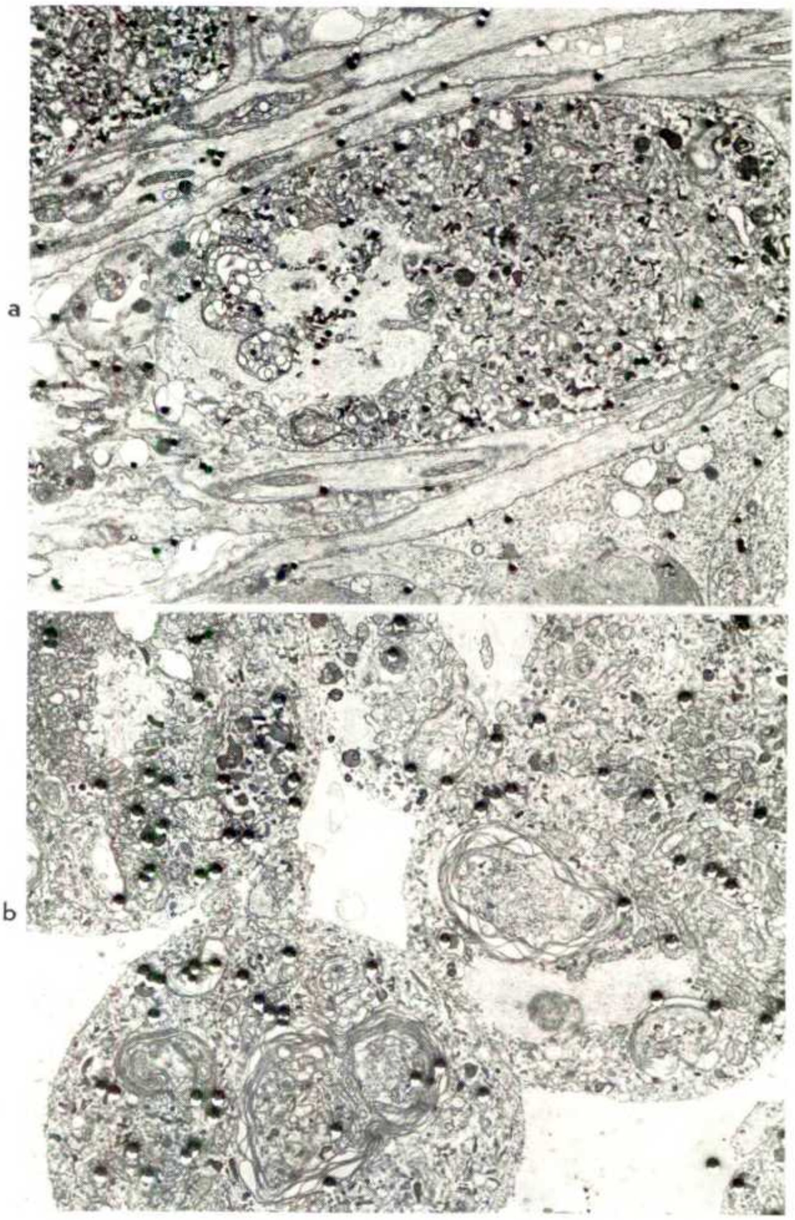

Fig 12 *(a) and (b) Electron microscopic autoradiographs from zone DZ of the ischaemic area in pig No. 3 (experiment B). The globular axon swellings were sectioned* (a) *along the axis of the axons, and* (b) *at right-angles to the axis of the axons. Both micrographs show many grains associated with these axon terminals.*
(a) × *5250;* (b) × *6500*

cells (McEwen and Grafstein, 1968; Chou, 1970; Hendrickson, 1972). To date ophthalmological research has been directed almost exclusively to obstruction of axoplasmic flow at the optic nerve head. Interruption of orthograde ^{3}H-leucine transport and an accumulation of organelles have been reported, for example, in experimental glaucoma and papilloedema (Anderson and Hendrickson, 1974; Tso, 1976), though the exact cause of the obstruction to axoplasmic flow in these conditions has not been identified. In our study obstruction of axoplasmic transport in axon segments *within the retina* was demonstrated by autoradiography; the findings are summarised in Fig. 14. In experiment A, in which ^{3}H-leucine was injected at the time of laser coagulation and arteriolar occlusion, label became concentrated in swollen axon terminals on the peripheral aspect of infarcts (PZ) but was absent from the distal axon terminals of zone DZ, indicating an obstruction to orthograde axoplasmic transport

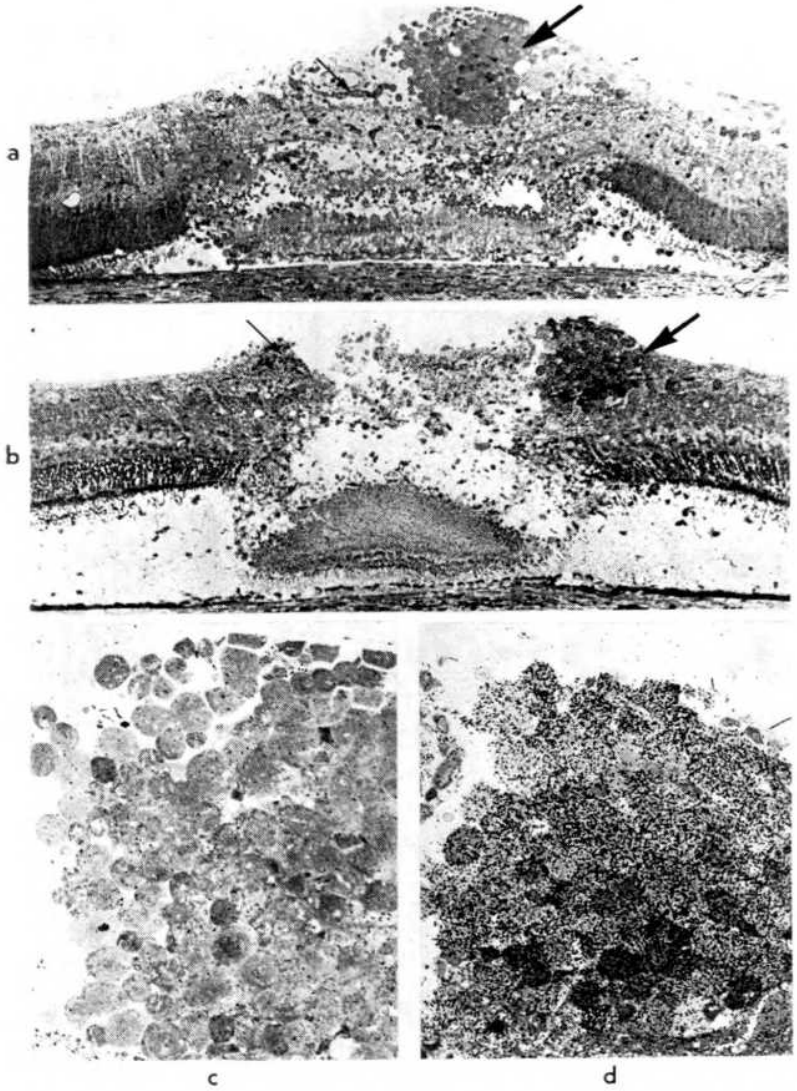

Fig. 13 *(a), (b), (c), and (d) Light microscopic autoradiographs of laser-induced lesions from experiment A ((a) and (c)) and experiment B ((b) and (d)); sections were cut along the axis of ganglion-cell axons.*

(a) *Autoradiograph showing the concentration of ^{3}H-leucine in PZ (fine arrow) and the absence of label in axon terminals in DZ (coarse arrow) in experiment A.*

(b) *Autoradiograph showing a high concentration of label in DZ (coarse arrow) as well as in PZ (fine arrow) in experiment B.*

(c) *High power light microscopic autoradiograph from the area DZ in Fig. 13 (a) (experiment A). The limited number of grains may be accounted for by glial uptake and background.*

(d) *High power light microscopic autoradiograph from the area DZ in Fig. 13 (b) (experiment B). An extremely dense concentration of grains is seen over the spheroidal axon terminals.*

(a) *and* (b) × *180;*
(c) *and* (d) × *330*

in axons damaged by ischaemia. In experiment B 2 days were allowed for ^{3}H-leucine to be incorporated within ganglion cells and become distributed throughout the axoplasm prior to laser occlusion (Chou, 1970; Hendrickson, 1972). Label became concentrated in axon swellings on both sides of the ischaemic areas after a further two days. Studies of a similar design were previously carried out by Lasek (1967) and Ochs (1975) using peripheral nerves, and the build-up of label in proximal and distal axon terminals was attributed to obstruction of orthograde and retrograde axoplasmic transport, respectively.

Shakib and Ashton (1966) considered that the various organelles which accumulate in axon terminals at the edge of retinal infarcts *proliferate* at this site in response to a hypoxic stimulus. However, in our experiment A the vitreal pool of ^{3}H-leucine was available to axon segments on both sides of the retinal infarcts, yet label concentrated in zone PZ but was absent from DZ. This finding is difficult to explain on the basis of intra-axonal organelle synthesis if we assume that the cause of organelle aggregation in DZ was the same as that in PZ. Shakib and Ashton (1966) argued against an interruption of the axoplasmic transport of organelles, citing the depletion of cytoplasmic constituents which they had observed in the axon hillock region of ischaemic ganglion cells. However, orthograde transport of organelles synthesised in ganglion cells *peripheral to* the infarct determines their aggregation in PZ, so axon hillock changes in ganglion cells *within* the infarct are irrelevant to this discussion.

There was some minor morphological variation in adjacent axon terminals within PZ and DZ 2 days after axonal injury, but striking differences were seen if axon swellings on opposite sides of infarcts were compared—that is, PZ compared with DZ. After 2 days' development the proximal swellings were elongated or tapered and contained relatively well preserved mitochondria (Fig. 5*a*), while distal terminals had a spheroidal shape and contained mitochondria in various stages of degeneration (Fig. 5*b*). This is a new observation in respect of focal retinal ischaemia, and probably reflects the fact that proximal axon terminals remain in dynamic communication with the perikaryon while the distal part of the axon is no longer so connected.

The axon terminals adjacent to retinal infarcts showed no significant difference in either shape or organelle content from those on each side of laser burns, and the autoradiographic findings were identical in each type of lesion; *the pathogenesis of axonal swelling was undoubtedly the same in each case*. While all axons passing through laser burns were totally and irreversibly disrupted, however, varying degrees of axonal injury were seen in relation to retinal infarcts. Axon terminals were typically found in the deeper parts of the nerve-fibre layer at the edge of infarcts, while some axons near the vitreal surface of the retina showed little morphological change, and continuing orthograde axoplasmic transport across the ischaemic area was demonstrated in these neurones. The maintenance of axonal structure and function beneath the inner limiting membrane was presumably due to metabolic exchange with the vitreous cavity (Tascopoulos *et al.*, 1976); this survival of some axons within small infarcts influences the effect of focal retinal ischaemia on visual function (McLeod, 1976).

NATURE OF RETINAL COTTON-WOOL SPOTS

Cotton-wool spots have been recognised as distinct ophthalmoscopic entities for over a century, yet the pathogenesis of these lesions has not been fully appreciated until now. Our studies indicate that cotton-wool spots should be regarded as localised accumulations of axoplasmic debris in the retinal nerve-fibre layer which result from interruption of organelle transport in ganglion-cell axons. Any factor responsible for focal interruption of axonal flow in the retinal nerve-fibre layer will give rise to similar accumulations, though clinically the cause is usually ischaemia (Fig. 15).

Dollery *et al.* (1966) had regarded the whole of ischaemic areas produced by microembolisation in pigs as 'cotton-wool spots'. However, our clinical and experimental observations demonstrate that no simple relationship exists between the size of the territory of an occluded vessel and the development of white (as opposed to grey) retinal swelling. The *length* of a cotton-wool spot (that is, the dimension at right-angles to the axis of ganglion-cell axons) reflects only the extent of that boundary of an ischaemic area which is crossed by retinal nerve fibres. The *width* of a cotton-wool spot (that is, the dimension along the axis of axons) depends on the distance that different axons penetrate an ischaemic area before axoplasmic transport is interrupted. The threshold of individual nerve fibres to anoxic damage is probably variable, and the local vitreal oxygen tension and capillary collateral blood flow may also be important in determining this dimension of the border zone. The *degree of swelling* and opacification of a cotton-wool spot reflects the amount of axoplasmic debris which accumulates; this is determined by the volume flow of axoplasm

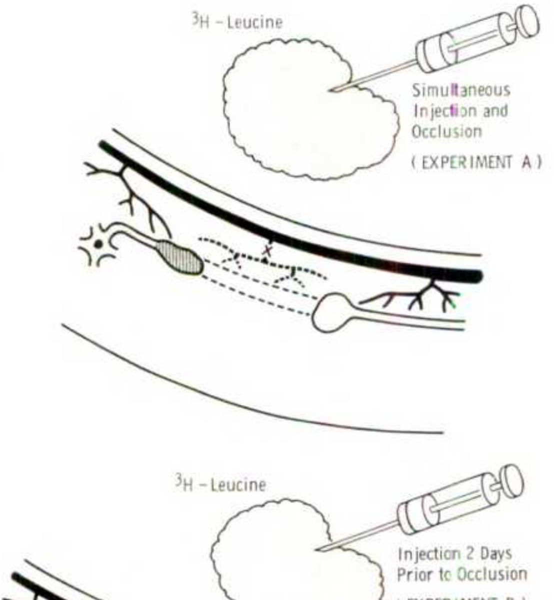
³H - Leucine
Simultaneous Injection and Occlusion
(EXPERIMENT A)
³H - Leucine
Injection 2 Days Prior to Occlusion
(EXPERIMENT B)

Fig. 14 *Summary diagram of autoradiographic findings*

and so depends mainly on the thickness of the nerve-fibre layer at the boundary between viable and ischaemic retina.

In conclusion, therefore, cotton-wool spots are not 'microinfarcts' of the inner retina, as defined hitherto. The intra-axonal aggregation of organelles which we observed 2 days after retinal arteriolar occlusion was not itself a manifestation of neuronal hypoxia, but was merely a sequel to anoxic disruption of normal physiological processes in the contiguous segments of the axons. The accumulation of cytoplasmic debris (and development of opaque retinal swelling) was thus as much a reflection of continuing axoplasmic transport in unaffected parts of axons as of ischaemic necrosis of axon segments within the retinal infarct.

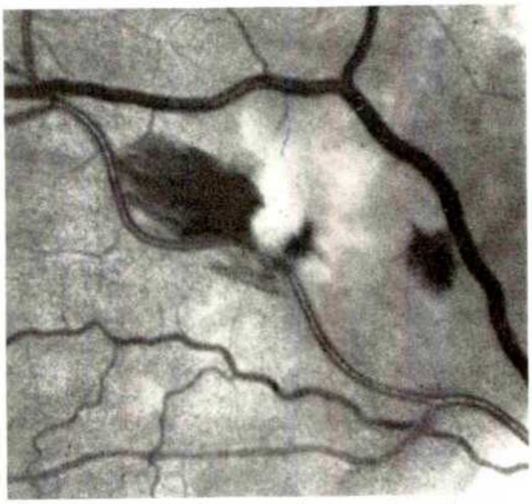

Fig. 15 *Ischaemic lesion in a hypertensive patient: accumulations of white axoplasmic material on each side of a small retinal infarct; part of the zone PZ is outlined by haemorrhage (Courtesy of Mr L. G. Fison)*

We thank Miss E. Clarke and Mr P. L. Ansell for their help in electron microscopy and autoradiography, and Dr C. M. Kemp for both adapting his microspectrophotometer and patiently scanning our samples. Messrs R. Humphrey, K. Sehmi, and T. Tarrant assisted in the production of the illustrations. We are indebted to Miss I. F. Miller for her assistance in the preparation of the manuscript.

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Variability in grading diabetic retinopathy from stereo fundus photographs: Comparison of physician and lay readers

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SUMMARY Two physicians and two lay readers were trained according to a detailed protocol in the grading of 17 lesions found in diabetic retinopathy by evaluation of stereo fundus photographs according to a modified Airlie House classification. Intraobserver and interobserver variability of these readers was assessed by two methods: weighted kappa, and frequency of agreement within one grade.

In general, physician readers were found to be less variable on replicate readings than were lay readers, and had slightly better agreement with each other than with the lay readers. The physiological significance of the direction and magnitude of the difference between physician and lay reader variability for individual lesions was often uncertain. Assessment of contribution to disagreement by individual readers was possible and permits future training directed at reducing disagreement to acceptable values.

Stereo fundus photography has become widely accepted as a means of documenting ocular pathology in therapeutic trials such as the collaborative Diabetic Retinopathy Study (Kupfer, 1973; Diabetic Retinopathy Study Research Group, 1976), in epidemiological studies such as the Framingham Eye Study (Kahn, 1973), and in clinical follow-up of patients as for suspected malignant melanoma lesions (Ganley and Comstock, 1973). The use of photographs offers several advantages over clinical evaluation, although these two methods must be considered complementary rather than competitive. First, photographs provide greater opportunity to standardise evaluation techniques and to assess and control variability. Secondly, photographs are permanent records of pathology which permit systematic re-evaluation by other observers and by other grading criteria.

Individual physician-patient relationships are still best served, logistically and professionally, by each physician making his own clinical assessment of pathology according to accepted standards and techniques. Concern for standardisation of evaluation and for control of variability increases in research which emphasises group or population characteristics. This research, using statistical or epidemiological methods together with clinical evaluation, is appropriate when studying diseases considered to have multiple causality, with each cause being less than completely deterministic.

Ophthalmological studies of this kind, with several thousand patients perhaps followed up through repeated examination, frequently have large numbers of photographs to be evaluated. The logistics of grading these photographs raises several important considerations. Are sufficient ophthalmologists available to grade these photographs according to protocol requirements of standardised training and evaluation? Are ophthalmologist readers an efficient use of a highly skilled manpower resource? Should each photograph be graded more than once? By different graders? What is meant by accuracy, when no independent, objective, standard evaluation exists? What measures of variability are useful and adequately informative? How much grading variability is acceptable in general, or in a particular study? If non-physicians grade photographs, does this economic advantage reduce the quality of the readings? Success of studies involving photograph evaluation depends on answers to some or all of these questions. Although these questions

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are deceptively simple, it is not surprising that they may not have simple answers. The complexity of analysis reflects to some extent the difficulty in summarising complex study material.

In any study where observations are made, the potential for examiner variability is present and deserves considerable attention (Koran, 1975a, b). This includes variability in repeated observations by the same examiner, as well as variability of observations among different examiners (Kahn *et al.*, 1975). To alleviate the economic and manpower problems when large numbers of photographs are to be evaluated, non-physician readers—often paramedical technicians—are at present employed to observe, grade, and record subjective and objective data. If lay readers without paramedical training can adequately evaluate and grade fundus photographs, this would further improve the economic and manpower considerations.

With the increasing use of non-physician readers, the potential for reader variability and reduced diagnostic accuracy is accentuated. Little information is available on the intraobserver (within observer) or interobserver (between observers) variability associated with reading fundus photographs by physician or non-physician readers, although the Diabetic Retinopathy Study is a potential source for such information.

The purpose of this paper is to present the results of a study designed, in a limited way, to compare lay readers with physicians for variability in grading stereo fundus photographs of patients with diabetic retinopathy. It is in a sense a pilot study, not intended to answer definitively all questions of interest with equal vigour; such an ambitious study may not be feasible. Rather, this study may provide insight into the magnitude and complexity of the problem, with examples of analytical methods and results which may be useful to those who develop and conduct large-scale studies using stereo fundus photographs.

Materials and methods

The classification and grading system for diabetic retinopathy presented at the Airlie House symposium (Davis *et al.*, 1969), and further developed for the collaborative Diabetic Retinopathy Study was modified slightly for use in the present study. Standard stereo fundus photographs were used to classify and grade 17 different types of lesions found in diabetic retinopathy: haemorrhages and/or microaneurysms, hard exudates, soft exudates, venous abnormalities, arteriolar abnormalities, intraretinal microvascular abnormalities, arteriovenous nicking, macular oedema, neovascularisation near the disc, neovascularisation elsewhere, fibrous proliferation near the disc, fibrous proliferation elsewhere, plane of proliferation, retinal elevation, preretinal haemorrhage, vitreous haemorrhage, and intraretinal haemorrhage. Intraretinal haemorrhage was added to this study because of its frequent occurrence in diabetic retinopathy, and because lay readers were observed in the training session to misclassify intraretinal haemorrhage as either dot haemorrhages or preretinal haemorrhages.

Each reader was instructed to compare 'unknown' stereo photographs with a set of standard photographs of varying severity for each of the above 17 lesions. Depending on the severity of each lesion, each photograph was given a numerical grade. If a particular lesion was not present, the photograph was given a grade of zero for that lesion. If there was a question whether the lesion was present or absent a grade of 1 was recorded. Grades 2 through 5 were used to indicate increasing severity in relation to their respective standard photographs. A grade of 8 was used when the appropriate field for viewing a particular lesion was not present on the photograph being graded. A grade of 9 was used when it was not determinable whether a lesion was present or not; this might occur when large vitreous haemorrhages or massive vitreous proliferation obscured underlying retinal features.

A comprehensive protocol was developed for use in training the lay readers as well as the physician readers. Each lesion was described in detail and in language the lay readers could understand, and complete instructions were provided on how to grade the photographs according to the modified Airlie House classification.

A set of diabetic stereo fundus photographs was obtained from the Boston University Ophthalmology Department files for training purposes. For 3 weeks one of the investigators (R.L.) instructed the lay readers for approximately two hours each day, and they did further independent study daily for an additional two hours. Each lay reader had use of a Donaldson stereo viewer, teaching photographs, standard photographs, and a copy of the protocol and classification scheme. The training period was not extensive as the lay readers could spend only half of each day on training, while the remaining time was spent performing regular office duties. The physician readers went through a less extensive period of training, also becoming familiar with the classification scheme and the various lesions of diabetic retinopathy.

A set of diabetic stereo fundus photographs was obtained from the University of Wisconsin Department of Ophthalmology for use as 'unknowns'. These 97 photographs represented one or more of the seven standard fundus fields (Davis *et al.*, 1969) from 14 patients with moderate to severe diabetic retinopathy. In addition 51 standard stereo photographs from 8 individuals without diabetic retinopathy were included as 'unknowns'. All photographs were taken with a fundus camera equipped with the Allen Stereo Separator.

Duplicate copies were made and randomly combined to form the full study group of 296 'unknowns'. Each stereo pair would then be evaluated independently of other fields in the same eye and of its duplicate pair. Each reader received the complete set of photographs in the same order but began at a different starting point. Since there were 17 conditions to be examined per stereo photograph, each reader made 5032 (17 × 296) readings.

Four readers participated in this study. Reader 1 was an opthalmologist with some experience in grading fundus photographs. Reader 2 was a physician with little ophthalmic background. Reader 3 was a secretary and Reader 4 a statistical clerk. Readers 1 and 2 knew the set of slides contained duplicates, but Readers 3 and 4 were not so informed, although at some point in the study they may have become aware of this fact.

The readers recorded their evaluations on coding forms which listed the various lesions to be evaluated, and which provided space for the reader's name, time reading began, time finished, and the identification numbers of the photographs being evaluated. When each reader finished a set of 10 photographs, the grades and photographs were returned and the next succeeding set obtained, thus preventing comparison with previous gradings. The data were keypunched and entered into the computer for editing and analysis. Minor inconsistencies in data collection discovered through editing were corrected.

MEASURES OF VARIABILITY

A variety of indices are available for assessing observer variability on categorical data described by ordinal scales (Landis and Koch, 1975). Choice of an index, while based partially on evaluation of suitability and informativeness for the problem at hand, is somewhat arbitrary since various properties of an index appeal differently to different users. Two methods were chosen for evaluation of intraobserver and interobserver variability in this study: weighted kappa (Cohen, 1968), based on the Rogot-Goldberg index of adjusted agreement (Rogot and Goldberg, 1966) (see appendix), and frequency of agreement within one grade.

In any study involving somewhat subjective observations some degree of interobserver and intraobserver variability is expected. Agreement within one grade was chosen to represent acceptable variability, while the complement—disagreement by more than one grade—was felt to represent a major degree of variability. For simplicity the few disagreements which involved non-ordered grades, i.e., 'wrong field' and 'not determinable', were omitted. The weighted kappa form of the Rogot-Goldberg index provides a measure which moderates the influence of artificially high agreement often observed when classifying rare phenomena, and which also readily permits statistical tests of significance. Weighted kappa (κ_w) may be described as the ratio of *observed* weighted agreement not accounted for by chance to *possible* weighted agreement not accounted for by chance. Thus $\kappa_w = 1$ indicates perfect agreement, $\kappa_w = 0$ chance agreement, and $\kappa_w < 0$ less than chance agreement.

Results

The average time spent in grading all 17 lesions on each slide was 2·5 minutes per slide for the 2 physician readers, 5 minutes for Reader 3, and 11 minutes for Reader 4.

INTRAOBSERVER VARIABILITY

An example of intraobserver (within observer) variation in grading microaneurysms and/or haemorrhages is given in Table 1. Reader 1, on the first reading, graded 61 of the fields as having 'moderate' haemorrhages and/or microaneurysms as compared to the standard for that lesion; on the second reading 48 were graded as 'moderate'. Only 44 were graded 'moderate' on both readings. In this example all readers had difficulty in characterising the lesion as 'minimal' or 'moderate'.

Weighted kappa index of agreement. Assessment of intraobserver variability by weighted kappa was based on two-way frequency tables, such as Table 1. Values of weighted kappa measuring percent agreement ($100\,\kappa_w$) between first and second readings for each reader for each of 16 lesions are given in Table 2 (κ_w was not computed for vitreous haemorrhage owing to its rare occurrence).

Both physicians showed better agreement between first and second readings for 9 of the 16 lesions than did either lay reader. In seven instances the minimum physician agreement exceeded the maximum lay reader agreement by at least 10%, with maximum exceedance of 34% occurring for retinal elevation, but these exceedances could have occurred by chance ($P > 0{\cdot}20$). For intraretinal haemorrhage both lay readers showed replicate agreement as good as or better than either physician.

For 15 of 16 lesions (all but intraretinal haemorrhage) the average physician agreement by weighted

Table 1 *Frequency of agreement between first and second reading of 148 fundus photographs for presence and severity of haemorrhages and/or microaneurysms, for 4 readers**

			First reading (grades)				
			Absent/ Questionable	*Present*			
	Grades	*Reader*†		*Minimal*	*Moderate*	*Severe*	*Total*
Second Reading	Absent/ Questionable	1	53	1	0	0	54
		2	55	4	0	0	59
		3	53	0	0	0	53
		4	41	13	0	0	54
	Present: Minimal	1	2	18	11	0	31
		2	2	23	5	0	30
		3	4	3	7	0	14
		4	8	23	5	0	36
	Moderate	1	0	4	44	0	48
		2	0	8	45	0	53
		3	0	2	67	6	75
		4	5	15	19	5	44
	Severe	1	0	0	6	9	15
		2	0	0	2	4	6
		3	0	0	0	4	4
		4	2	0	3	9	14
	Total	1	55	23	61	9	148
		2	57	35	52	4	148
		3	57	5	74	10	146
		4	56	51	27	14	148

Reader†	*Weighted kappa (%)*
1 Ophthalmologist	76
2 Physician	78
3 Secretary	66
4 Clerk	50

*Readings 'wrong field' and 'not determinable' are omitted.

kappa was greater than that for lay readers. In nine lesions the difference in weighted averages was at least 20%, a statistically significant difference ($P < 0{\cdot}02$) for haemorrhages and/or microaneurysms and plane of proliferation. The maximum difference in averages was 49% for retinal elevation. Retinal elevation also had the greatest range of weighted kappa (65%), and nine lesions had ranges greater than 25%.

Rank comparison by Friedman's two-way analysis of variance* strongly suggests the readers differ in variability ($\chi^2_3 = 18{\cdot}0$, $P < 0{\cdot}001$). The magnitudes of the average ranks suggest that the physicians exhibited less variability in agreement than did the lay readers and further that the lay readers exhibited about equal variability.

Agreement within one grade. The frequency with which a reader agreed with himself within one grade on replicate readings is given in Table 2. For 9 of 17 lesions both physicians showed better agreement between first and second readings than did either lay reader. In two of these lesions (soft exudates and retinal elevation) the maximum lay reader agreement was at least 10% less than the minimum physician agreement. For intraretinal haemorrhage both lay readers showed equal or better agreement than either physician.

Analysis of variance by ranks of agreement percentages gives results similar to that for the index of agreement. Maximum range for percent agreement is 29% (fibrous proliferation of disc), and four lesions have ranges greater than 20%. For 14 of 17 lesions the average lay reader percent agreement is less than that for physicians; in 5 cases the difference in averages is at least 10%, with maximum of 24% for retinal elevation. Physician agreement varied from 86 to 100%, with average agreement of 96% for each physician. Lay reader agreement varied from 71 to 100%, with averages of 91 and 85% for Readers 3 and 4, respectively.

INTEROBSERVER VARIABILITY

Weighted kappa index of agreement. Assessment of interobserver (between observers) variability by average weighted kappa is given in Table 3. Agreement was better between physicians than between

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*For each of the 16 lesions, the indices for each abnormality were assigned ranks from smallest to largest (1 to 4) for the readers. The null hypothesis is that the average rank over the 16 lesions (or, equivalently, the distribution of ranks for a reader) does not depend on the reader.

Table 2 *Intraobserver variability assessed by comparison of first and second readings of 148 fundus photographs for 17 diabetic retinopathy lesions among 4 graders by 'weighted kappa' and 'agreement within one grade'*

Lesion	*Agreement by weighted kappa (%) Readers*				*Agreement within one grade (%) Readers*			
	Physicians		*Lay readers*		*Physicians*		*Lay readers*	
	1	*2*	*3*	*4*	*1*	*2*	*3*	*4*
Haemorrhages and microaneurysms†	76	78	66	50	98	96	97	82
Hard exudates	70	82	67	61	94	97	87	96
Soft exudates†‡	82	85	54	48	100	99	84	80
Venous abnormalities	72	69	55	76	95	89	87	89
Arteriolar abnormalities	74	64	64	72	95	88	95	88
Intraretinal microvascular abnormalities	50	72	59	36	93	97	87	75
Arteriovenous nicking	66	76	66	73	95	91	94	92
Macular oedema*	49	74	55	49	86	90	86	76
Neovascularisation near the disc*	65	83	60	37	95	100	100	76
Neovascularisation elsewhere†	90	87	66	56	97	95	94	82
Fibrous proliferation near the disc*†	100	100	69	58	100	100	95	71
Fibrous proliferation elsewhere†	85	84	64	62	98	96	95	91
Plane of proliferation	59	76	76	33	93	94	92	84
Retinal elevation†‡	75	100	35	41	99	100	72	78
Preretinal haemorrhage†	100	81	66	59	100	100	97	89
Vitreous haemorrhage	nc	nc	nc	nc	100	100	86	98
Intraretinal haemorrhage	88	94	93	94	94	97	97	97
Average	75	82	63	57	96	96	91	85
Average rank	2·8	3·4	2·0	1·7	3·2	3·1	2·1	1·5

*Based on only those (21) slides which include the appropriate field (disc or macula).

†Minimum physician agreement exceeds maximum lay reader agreement by at least 10%, for weighted kappa.

‡Minimum lay reader disagreement exceeds maximum physician disagreement by at least 10%, for disagreement by more than one grade.

nc—Not computed, since lesion was extremely rare.

Table 3 *Interobserver variability among 4 graders of 148 fundus photographs for 16 diabetic retinopathy lesions as measured by the average weighted kappa*¶

Lesion	*Average agreement between readers (%)*					
	Ophthal/ Physician	*Secretary/ Clerk*	*Ophthal/ Secretary*	*Ophthal/ Clerk*	*Physician/ Secretary*	*Physician/ Clerk*
Haemorrhages and microaneurysms‡	66*	47†	63	54	63	52
Hard exudates‡	66*	39†	54	62	47	59
Soft exudates‡	67*	42	36	11†	39	29
Venous abnormalities	57	48†	51	58*	52	54
Arteriolar abnormalities‡	49	36	34†	34	36	50*
Intraretinal microvascular abnormalities‡	46*	17	29	14	5†	10
Arteriovenous nicking	54*	48	50	42†	48	53
Macular oedema§	22	19	17	46*	30	1†
Neovascularisation near the disc§	21	41	69*	39	43	18†
Neovascularisation elsewhere‡	73*	54	63	54†	60	60
Fibrous proliferation near the disc§	50	40	85*	39	56	13†
Fibrous proliferation elsewhere	66*	56†	59	48	57	60
Plane of proliferation‡	43*	18	14	9†	41	18
Retinal elevation‡	88*	19	36	–4†	37	11
Preretinal haemorrhage‡	80*	53	69	57	65	47†
Intraretinal haemorrhage	89	88	87	81†	93*	88
*/†:	10/0	0/4	2/1	2/6	1/1	1/4

For each lesion, *indicates greatest agreement; †indicates least agreement.

‡Physician agreement exceeded lay reader agreement by at least 10%.

§Based on only those (21) slides which include the appropriate field (disc or macula).

¶When comparing two readers who have two replicate readings, it is possible to compute two independent estimates of weighted kappa. The average of these two values is a single measure of agreement which includes information from replication.

lay readers (column 1 *v.* column 4) for all lesions except neovascularisation of disc, with maximum difference in agreement for retinal elevation (69%). For 9 of 16 lesions physician agreement exceeded lay reader agreement by more than 10%, a statistically significant exceedance ($P<0{\cdot}05$) for haemorrhages and/or microaneurysms, hard exudates, and plane of proliferation.

Agreement between physicians (column 1) exceeds the best agreement between either physician and a

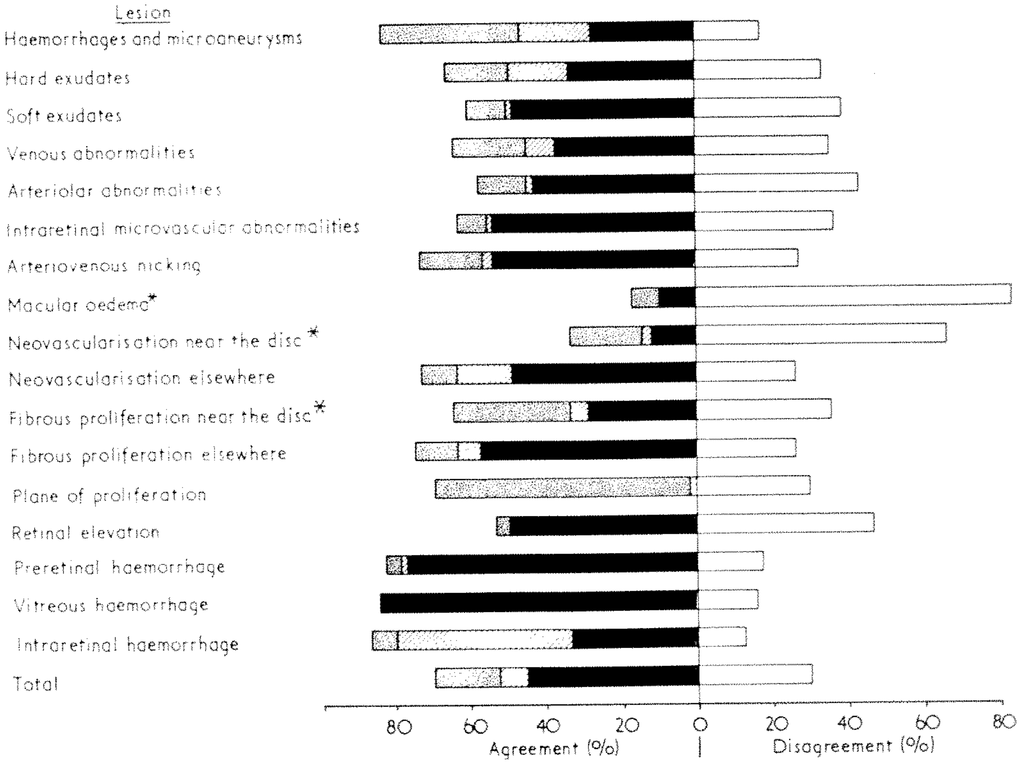

Fig. 1 *Interobserver variability among 4 graders of 148 fundus photographs for 17 diabetic retinopathy lesions according to percentage of 148 photographs where the readers:*
(a) *all agree on a negative reading (solid bar)*; (b) *all agree on a positive reading (striped bar)*; (c) *give readings on two adjacent grades (dotted bar)*; *and* (d) *disagree by more than one grade (clear bar)*

*Percentages based on only those photographs (21) which include the appropriate field (disc or macula).

lay reader (columns 3 through 6) by at least 10% for 5 lesions—soft exudates, intraretinal microvascular abnormalities, neovascularisation elsewhere, retinal elevation, and preretinal haemorrhage—with maximum exceedance 51% for retinal elevation. Conversely, the best agreement between a lay reader and either physician exceeds the agreement between physicians by at least 10% for three lesions—macular oedema, neovascularisation, and fibrous proliferation near the disc—with maximum exceedance of 48% for neovascularisation near the disc.

AGREEMENT WITHIN ONE GRADE

Fig. 1 shows for each lesion the percentage of photographs in each of 4 agreement-disagreement categories, averaged over the two replicate readings: *(a)* all readers agree on a negative reading; *(b)* all readers agree on a positive reading; *(c)* all readings are of two adjacent grades; and *(d)* disagreement by more than one grade. Most categories, and in particular category *d*, were quite similar for the two replicates. Agreement for all lesions combined was 70%, ranging from 88% (intraretinal haemorrhage) to 17% (macular oedema). Agreement exceeded 70% in the grading of 8 of 17 lesions.

Fig. 2 shows for each lesion the percentage of cases of agreement in the first replicate reading for which each reader was a contributor to the disagreement. Results for the second replicate reading were similar except as noted below. The relative contribution to disagreement was essentially the same for the four readers in 3 lesions: arteriovenous nicking, plane of proliferation, and intraretinal haemorrhage. In no case did a physician contribute excessively to disagreement. Both lay readers contributed noticeably to disagreement in contrast to the physicians for soft exudates and retinal elevation. Reader 3 was the primary contributor for hard exudates, macular oedema, and vitreous haemorrhage disagreement; Reader 4 was so for 9 lesions, although for 2 lesions (haemorrhages and/or microaneurysms, fibrous proliferation of disc) this result was not true for the second replicate readings. Overall, the physicians each contributed to 18% of the disagreements, Reader 3 to 27%, and Reader 4 to 37%.

Discussion

While absence of variability is ideal, some variation must be accepted as real in any clinical or laboratory measurement. The nature and magnitude of the variability should be assessed and presented routinely with study results, to allow users of the results to form their own judgments of the reliability of the data. General rules defining maximum acceptable variability have never been formulated; rather, the level of acceptable variability should be considered in light of the study procedures and goals. The importance of differences in performance among readers must also be evaluated in terms of the use to be made of the grades assigned to the lesions, whether in some composite score for an individual eye or on a per lesion basis, for discrimination among groups of individuals (eyes) or for assessing changes in a given eye over time.

Sources of variation in reading fundus photographs include differences in stereoviewer models (optics, illumination, interpupillary distance), reader factors (poor stereopsis, glare intolerance, fatigue threshold), and interaction between photograph quality and reader, in addition to the variability of reader judgment. In some instances the 'unknown' lesion was difficult to evaluate, or was intermediate between two standards and could easily have been given either adjacent grade. The training of the readers was designed to minimise this variation, but how well this was achieved could not be determined. Reader variability includes a contribution from these and other unrecognised factors, the resultant effect being one of overall variability in grading, usually without readily discernible components that may differentially affect readers.

Intraobserver variability as measured by weighted kappa and percent agreement showed physician readers to be less variable overall than lay readers. Soft exudates and retinal elevation were clearly marked as requiring additional training for both lay readers. Assessment by weighted kappa suggested a need for additional lay reader training in 7 lesions which had at least 10% difference between physician and lay readers, and pointed out specific areas of weakness for all readers (e.g., macular oedema and intraretinal microvascular abnormalities for the ophthalmologist). For Reader 4 other lesions were marked for improvement in reliability of grading relative to the other readers, by one or both measures of variability: haemorrhages and/or microaneurysms, intraretinal microvascular abnormalities, neovascularisation of the disc, neovascularisation elsewhere, fibrous proliferation of disc, and plane of

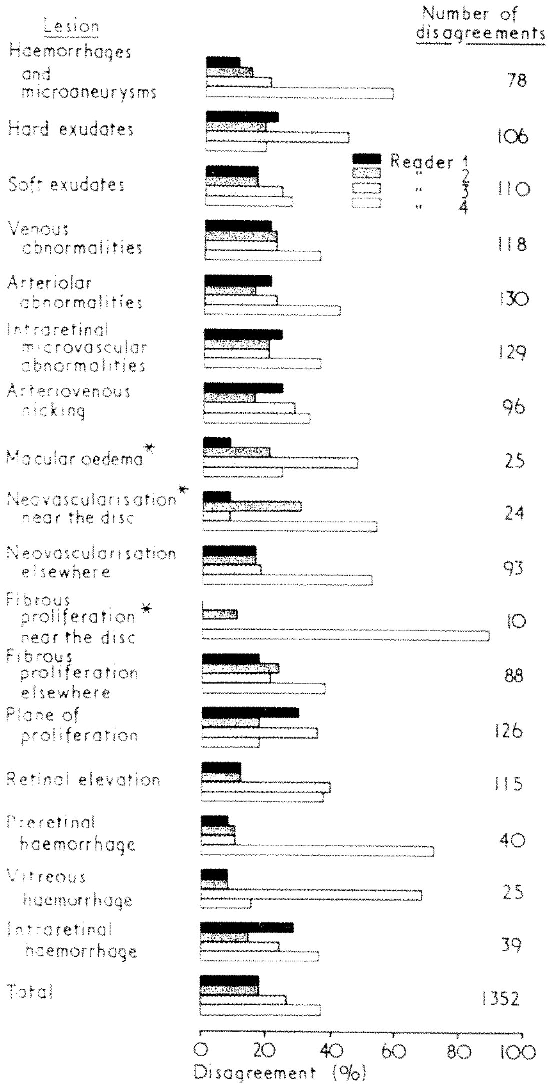

Fig. 2 *Relative contribution to disagreement by each reader for 17 diabetic retinopathy lesions, for first replicate readings of 148 photographs. Readers 1 and 2 are physician readers; Readers 3 and 4 are lay readers. Disagreement includes cases where the range of readings for the four readers is greater than one grade, and cases where three readers agree on a grade but the fourth differs by one grade*

*Based on only those photographs (21) which include the appropriate field (disc or macula).

proliferation. The intraobserver variability observed in this study is probably less than would be found if the replicate slides were graded after an interval of time.

Physician-lay reader differences, although statistically significant, may often be of a magnitude to which it is difficult to assign physiological or practical importance. Nevertheless, when these differences are considered for all readers, the range of variability observed for a particular lesion may be of sufficient concern to attempt reduction through additional training or modification of the protocol; or to accept the fact that perhaps some lesions do not readily submit to a repeatable grading system and should be dropped from the study.

Percent disagreement as given in Fig. 1 is perhaps more useful because it permits assessment of the joint performance of all four readers, for each lesion. While macular oedema and neovascularisation of disc are also clearly marked as showing excessive disagreement among readers, this measure also points to at least seven other lesions where additional attention and training would be required to achieve desirable operational agreement. Analysis as shown in Fig. 2 permits a more detailed discrimination among readers in terms of requirements for additional training and would be most useful in refinement of the grading protocol before actual application to clinical or epidemiological data.

In addition to determining the intraobserver and interobserver variability of physicians and lay readers in grading fundus photographs for diabetic retinopathy part of the intent of this study was to determine the level of training required in order to train lay readers adequately to evaluate and grade stereo fundus photographs for particular abnormalities. For this purpose two individuals with different backgrounds and ability were selected. Reader 3 was a college graduate who was an executive secretary. Reader 4 was a statistical clerk with a high school education and trained in data processing. Although both individuals dealt peripherally with ophthalmic terminology, neither had any basic knowledge of either normal or morbid ocular anatomy. In spite of the minimum amount of training both lay readers became reasonably skilful in grading lesions. Although additional training for the readers and lesions identified with high variability was not undertaken as would normally have been done if production grading were the goal of the study, it is reasonable to assume that such training would be beneficial.

Grading of fundus photographs by lay readers has distinct advantages over the use of physicians. In addition to freeing valuable physician time, well-trained lay readers may be more systematic, objective, and conscientious. The ophthalmologist (J.P.G.) indicated that he hurried through the slides in order to get on to more interesting pursuits. This no doubt increased his variability.

Lay readers were less efficient, requiring 2 to 4 times longer to read the slides as compared to physician readers. This time should decrease with increased training and experience. Shorter physician reading time must be balanced by the fact that physician cost per reading is higher than for lay readers, and that physicians could be more effectively employed in other areas equal to their training. Adequate checks can be used to monitor lay reading, such as random samples of photographs independently read by physicians, and replicate readings.

Certain abnormalities of diabetic retinopathy were found to be more difficult to evaluate and grade than others, emphasising the need for continuing surveillance to identify weak areas early and attempt to strengthen them. One lesion in particular, macular oedema, was the source of large reading variation for both physicians and lay readers, probably due to the technique used in this study for reading the photographs. The stereo slide pair was removed from the plastic filmholder and placed in the Donaldson stereoviewer, which had been modified to handle independently mounted 35-mm slides. The distance between the slide pair could vary in the holder. A wide separation of the slides at the extreme of fusion often gave a sensation of macular elevation which might be interpreted as macular oedema. Similarly, variation in slide separation also gave varying degrees of retinal elevation and planes of fibrous proliferation.

Lay readers had particular difficulty with fundus pathology not covered in the protocol or training slides: chorioretinal lesions, disciform macular degeneration, vein occlusion, etc. They also took the written protocol very literally. For example, arteriolar strands were described as thin white lines. An unknown slide which had a somewhat prominent straightened choroidal pattern was misclassified by one of the readers as arteriolar abnormalities. In training lay readers it is necessary to have standard photographs covering a wide range of normal anatomy and of pathological conditions other than diabetic retinopathy to help them differentiate diabetic abnormalities from other non-diabetic changes.

Although interobserver agreement is not entirely synonymous with accuracy, observer agreement is a major component. In the absence of an absolute standard to determine accuracy the subjectivity in a grading scheme such as used in this study demonstrates that accuracy may be a difficult concept to describe. Agreement between physicians is for some lesions less than agreement between lay reader and physician, e.g., macular oedema, and neovascularisation and fibrous proliferation near the disc. Several methods have been devised to handle observer disagreements, such as adjudication by a third reader when two readers disagree, or by calculating the mean or median of two or more independent readings. Discussion of these approaches and the definition of accuracy is beyond the scope of this study.

Mr Harold A. Kahn, Office of Biometry and Epidemiology, National Eye Institute, suggested this study and provided help and encouragement during its conduct; Alma Green and Frances Cryan participated as lay readers; Dr Howard Leibowitz, Boston University Ophthalmology Department, provided training slides; and Dr Matthew Davis, University of Wisconsin Ophthalmology Department, provided the basic grading system, standard fundus photographs of diabetic retinopathy, and study slides.

Appendix: Weighted kappa

RATIONALE

A common index of agreement for comparing the performance of 2 readers, or of 1 reader with himself, when classifying items, is the proportion of the total number of observations that are in agreement. However, in conditions such as vitreous haemorrhage, which occurs infrequently, the large number of 'absent' grades, on which there is usually little disagreement, will give an artificially high index of agreement. This index of crude agreement can be further misleading, since quite dissimilar patterns of agreement can give rise to identical measures of agreement. The Rogot-Goldberg (R-G) index of adjusted agreement, on the other hand, reflects more of the influence of individual sub-categories on the total agreement, giving more weight to smaller numbers and diminishing the effect of the larger groups. This index can be used to compare repeated readings by the same observer, or readings of 2 different observers.

The number of points in the ordinal scale used to grade a lesion varied by lesion. Further differences in the ordinal scales were created when scale values were grouped to ensure that all marginal totals (or frequencies) were non-zero, as required for computation of the R-G index. The codes for 'wrong field' and 'not determinable' were omitted as being non-ordinal, with what is judged to be a negligible effect on the analyses. The 'absent' and 'questionable' codes were combined in all lesions, since 'questionable' rarely occurred. The result of this grouping was categorisation into 2- to 4-point ordinal scales.

The chance value of the R-G index, the percentage agreement expected under total independence of the 2 observers or observations being compared, is 1/L for an L-point scale. Since the magnitude of departure from chance agreement is relevant in evaluating both the strength of agreement and the difference between two indices, an adjustment for departure from chance is required. This is accomplished by weighted kappa, κ_w, the proportion of weighted agreement corrected for chance. A further benefit from this adjustment is that the sampling distribution of κ_w is approximately normal for large samples (Cohen, 1968; Fleiss, Cohen and Everitt, 1972).

COMPUTATION

When n subjects or items are classified by each of 2 observers on an L-point scale, agreement between the 2 classifications may be based on the data as summarised in an $L \times L$ table of observed proportions, with entry p_{ij} the proportion of items classified by observer (1) into category i and by observer (2) into category j, $\Sigma\Sigma_{ij} = 1$. Crude agreement is the measure $p_o = \Sigma\, p_{ii}$.

For a specified set of weights $\{w_{ij}\}$, $0 \leqslant w_{ij} \leqslant 1$, $p_o^* = \Sigma\Sigma\, w_{ij}\, p_{ij}$ is a weighted observed proportion of agreement. The weighted proportion of agreement expected under total independence of the two classifications is $p_e^* = \Sigma\Sigma\, w_{ij}\, p_{i\cdot}\, p_{\cdot j}$, where $p_{i\cdot}$ and $p_{\cdot j}$ are column and row marginal proportions. Weighted kappa, or weighted agreement chance corrected, is defined as $\kappa_w = (p_o^* - p_e^*)/(1 - p_e^*)$ and has approximately a normal distribution with large sample variance given by Fleiss, Cohen and Everitt (1972).

The Rogot-Goldberg index of adjusted agreement (Rogot and Goldberg, 1966) is p_o^* with the weights $w_{ii} = (1/p_{i\cdot} + 1/p_{\cdot i})/2L$, $w_{ij} = 0$ for $i \neq j$. In this case, $p_e^* = 1/L$ is expected, or chance agreement.

EXAMPLE

From Table 1, for Reader 1 the 4×4 table of observed proportions p_{ij} and marginal proportions based on first and second readings of the photographs according to an $L = 4$ point scale is as follows:

	First reading *Grades:*	*1*	*2*	*3*	*4*	*Total*
	1	53/148	1/148	0	0	54/148
Second	2	2/148	18/148	11/148	0	31/148
reading	3	0	4/148	44/148	0	48/148
	4	0	0	6/148	9/148	15/148
	Total	55/148	23/148	61/148	9/148	1

Crude agreement: 124/148 = 0·84

Rogot-Goldberg (R-G): $p_o^* = 0{\cdot}82$

Expected agreement: $p_e^* = 0{\cdot}25$

Weighted kappa: $\kappa_w = (0{\cdot}82 - 0{\cdot}25)/0{\cdot}75 = 0{\cdot}76$

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Primary vitrectomy as a preventive surgical procedure in the treatment of severely injured eyes

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SUMMARY The results of treating 72 severely injured eyes by primary vitrectomy combined with anterior and posterior segment reconstruction are presented. This approach aims at improving the visual prognosis by allowing fundus examination and immediate retinal surgery where indicated, and by preventing the more severe complications associated with vitreous and anterior segment disorganisation. The prospects for improved visual results and the problems encountered, particularly secondary haemorrhage, are discussed.

In some modern industrialised communities as many as 30% of all acute ocular cases attending hospital are due to injury (Minton, 1949), and ocular trauma accounts for 12% of all ophthalmic patients requiring hospital admission (Holland, 1964). Though perforating ocular injuries differ widely in type and severity, they carry a high risk of significant and permanent visual morbidity (Glees and Kleinhans, 1962; Avedikian and Simon, 1972; Heimann, 1972; Boudet *et al.*, 1973; Watz and Reim, 1973). A knowledge and understanding of the principles involved in the management of ocular trauma can therefore make an important contribution to an ophthalmologist's therapeutic effectiveness.

Recovery of an eye from injury depends on 3 factors (Roper-Hall, 1969): *(a)* Degree of initial damage; *(b)* efficiency of early treatment; *(c)* satisfactory management of complications.

The ophthalmologist cannot influence the severity of injury in eyes that present acutely for treatment in the accident department, but his judgment as to whether an eye is irreparably damaged or not is clearly decisive at this initial stage. Immediate enucleation of severely traumatised eyes, without attempts at repair, was previously a widespread practice. It was based firstly on fear of sympathetic ophthalmitis and secondly on scepticism as to the likelihood of a worthwhile outcome. The difficulty in formulating an accurate prognosis on the basis of the initial examination findings, the preservation of vision in apparently devastated eyes (Heath, 1954), and the fall in the incidence of sympathetic ophthalmitis with modern surgical techniques and post-operative care (Brauninger and Polack, 1971) have all added support to the move away from such an approach (Paton and Goldberg, 1968). The idea that visual results and freedom from complications should be taken as criteria of successful treatment, rather than the percentage of enucleations, is now widely accepted.

Statistics showing the results of treating perforating injuries indicate that improvement has taken place both in terms of retention of cosmetically satisfactory eyes and, more important, visually useful ones. Examination of the series of cases presented by Moncreiff and Scheribel (1945) and by Snell (1945) shows that the number of eyes blinded or enucleated was nearly twice the number of those retaining a vision of 6/60 or better. A reversal of this overall situation is shown by the results of the more recent series of Remky *et al.* (1967) and Watz and Reim (1973).

Developments underlying this change include the effective treatment of infection with antibiotics and the control of inflammation with steroids. Microsurgical techniques ensure more precise placement of sutures and accurate apposition of wound edges (Harms and Mackensen, 1967; Mackensen and Eberwein, 1972), challenging the surgeon to restore normal anatomy (Roper-Hall, 1969) or to reconstruct a functionally useful organ, utilising the remaining viable tissues.

In managing the more severe perforating injuries involving lens and vitreous, the conservative surgical techniques of abscission of prolapsed tissue and wound suture are insufficient to prevent complications which ultimately lead to severe visual impairment (Johnston, 1971; Boudet *et al.*, 1973). These include chronic non-infective uveitis, phakoanaphylactic uveitis, reactionary haemorrhage, fibrous

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overgrowth, glaucoma, hypotony, vitritis, vitreous strand formation, and retinal detachment (Duke-Elder and MacFaul, 1972).

The concept that a mixture of damaged lens material and vitreous was a potent influence, promoting chronic intraocular inflammation, cyclitic membrane formation, vitreous strand formation, retinal detachment, hypotony, and phthisis led Kasner (1968) to formulate a more forthright approach to surgical management. In aiming to avoid the development of such complications, the surgical emphasis was being shifted from the primarily preservative in the direction of the preventive. Where appropriate this involved enlargement of the corneal wound, complete removal of all damaged lens material, combined with anterior vitrectomy. Such measures effectively removed damaged and potentially harmful anterior segment tissues and also, by removing the vitreous, eliminated the substrate in which strand formation might otherwise have subsequently taken place. This view of the pathogenesis of post-traumatic intraocular complications has received clinical and pathological support (Coles and Haik, 1972).

Based on these considerations, the treatment of severe injuries at Freiburg University Eye Clinic has undergone modification with the aim of achieving a primary reconstruction of the globe at the initial surgical procedure (Faulborn and Birnbaum, 1974). Particular emphasis is laid on the following points: *(a)* Adequate exposure of the injured structures to enable thorough assessment of the extent of the damage; *(b)* removal of all traumatised tissue liable to act as a stimulus, source, or medium for intraocular inflammatory activity, fibroblastic activity, or neovascularisation; *(c)* reconstruction carried out using only structurally viable tissues; *(d)* visualisation of the posterior pole, so that reparative procedures to retinal tears, dialyses, etc., can be carried out.

The purpose of this study is, firstly, to present the results obtained after managing 72 severely injured eyes in this manner; secondly, to try to evaluate what benefits such methods bring in terms of the visual results obtained and the complications encountered in comparison to more conservative techniques; and, thirdly, to endeavour to define more clearly the problems encountered in treating such eyes, thus highlighting areas for further investigation.

Materials and methods

The material for this study comprised 71 patients (72 eyes) with severe perforating ocular injuries treated at the Freiburg University Eye Clinic between 1970 and 1975. In selecting cases for inclusion, a severe injury was defined as a perforation of the corneo-scleral envelope, resulting in prolapse or loss of intraocular contents and involving in addition damage to 2 or more intraocular structures. In practice the intraocular structures invariably damaged were lens and vitreous, together with other tissues in the majority of cases.

All cases were selected on the basis of the extent of the damage sustained by the affected eye, and this made for a somewhat more homogeneous group than is included under the heading 'perforating injuries' in many other published series.

Surgery was performed under general anaesthesia using a Zeiss Mk. 6 microscope, and descriptions of the procedure are published in detail elsewhere (Mackensen and Faulborn, 1974; Faulborn and Birnbaum, 1974). The great majority of cases included here were operated on and managed by the same surgeon (J.F.), this course ensuring a standardised technique and approach. Vitrectomy was by the open-sky method, in the early cases using Kasner's cellulose sponge technique, and later with a vitreous suction cutter apparatus designed at the Freiburg clinic (Hennig *et al.*, 1972). In order to acquire accurate information follow-up examination was carried out on 45 patients; 15 patients were not recalled because the eye either had been enucleated or was blind from already documented causes. 11 patients could not be contacted.

The examination consisted of measurement of corrected visual acuity, assessment of the visual field, slit-lamp examination, tonometry, examination of the vitreous cavity and retina with the Goldmann triple mirror, fundus examination by indirect ophthalmoscopy with indentation, fluorescein angiography, and ERG.

Results

The follow-up period of treated patients extended over a maximum of 6 years 2 months. No patient with a follow-up of less than 6 months was included, and the average follow-up time was 3 years 6 months.

AGE AND SEX DISTRIBUTION

Of the 71 patients 54 (76%) were male and 17 (24%) female. The age distribution histogram (Fig. 1) shows that severe injuries affect predominantly younger people, 24% of cases occurring in those aged 11 to 20 and 73% in those under 40 years of age. This preponderance in children (Kobor, 1965) and young adults (Glees and Kleinhans, 1962; Holland, 1964) is already well recognised and documented.

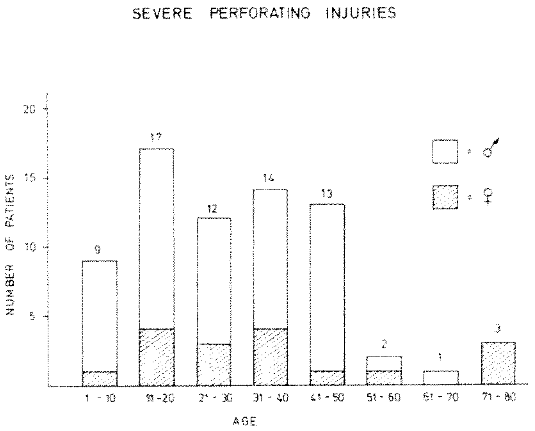

Fig. 1 *Distribution of patients according to age and sex*

CAUSE AND TYPE OF INJURY

Table 1 shows a statistical breakdown of cases in this series according to the activities and location of the patients at the time they sustained injury. Occupational activities predisposed to 44% of injuries. Road traffic accidents (RTA) formed the next largest group, and in comparison with other series (Roper-Hall, 1959) form a much larger proportion of cases. Compulsory wearing of seat belts and the imposition of lower speed limits can be expected to reverse this trend (Müller-Jensen and Allmaras, 1968; Johnston, 1971).

Table 1 *Activity or location at time of injury*

		(%)
Industrial occupation	26	(36)
Road traffic accident	18	(25)
Sport, play	12	(17)
House, garden	10	(14)
Farming, forestry	6	(8)
	72	(100)

Table 2 *Types of perforating injury*

		(%)
I: Blunt injury producing rupture	8	(11)
II: Sharp injury	43	(59)
III: Perforation with IOFB	21	(30)
	72	(100)

Perforating injuries can be grouped into three categories according to the type of implement or material directly responsible (Table 2). Each type of injuring agent tends to have fairly specific mechanical effects on the eye, producing patterns of structural damage and posing surgical problems requiring particular techniques and equipment for their solution. Knowledge of the circumstances surrounding production of the injury has clinical relevance in planning the surgical approach to primary reconstruction of an injured eye. Consideration of the activity or location where the different types of injury occur shows that 83% of severe perforating injuries resulting from road traffic accidents were sharp penetrating ones, usually windscreen glass, and that 50% of severe perforating industrial injuries were from intraocular foreign bodies (IOFB), mostly magnetic. Fig. 2 shows the frequency of particular injuries in the different locations and indicates where eyes are especially at risk. Thus, 61% of all IOFBs occur in industry, 39% of all blunt injuries in the house or garden, and the largest proportion of sharp perforations (34%) as a result of RTAs. Such figures assist in planning an intensification in the effectiveness of preventive measures, such as seat belts, protective goggles,

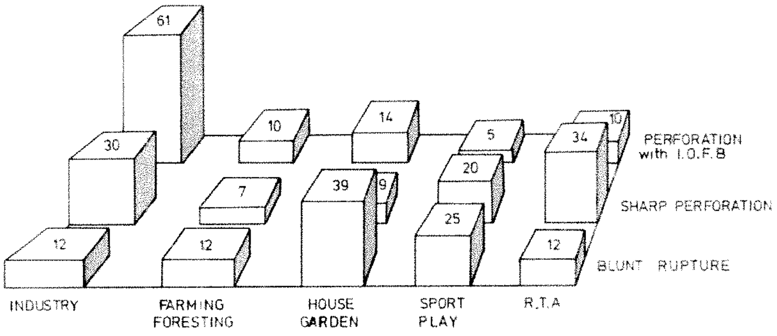

Fig. 2 *Relationship between type of injury and the location in which it is sustained*

The figures on the columns give the frequency (%) with which the given type of injury occurs in the different locations e.g. 61% of all I.O.F.B perforations are industrial.

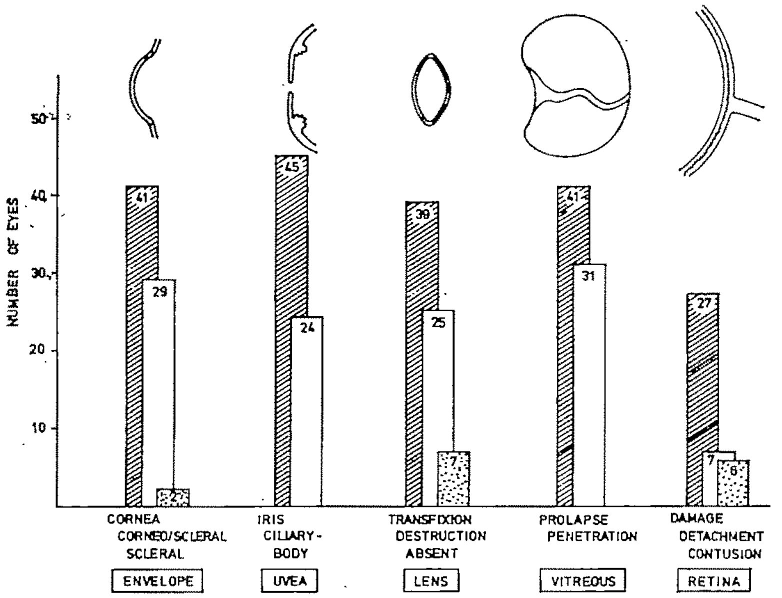

Fig. 3 *Documentation of injured ocular structures*

etc., and underline the arguments in support of concentrating the sophisticated equipment for detection and extraction of IOFBs in centres serving highly industrialised areas.

STRUCTURES AND TISSUES INJURED

Painstaking assessment of the structural damage sustained by each injured eye is an essential first stage in primary reconstruction, great care being taken not to cause further insult to the tissues, a procedure possible only by using the microscope. Fig. 3 shows that the lens and vitreous were damaged in all the cases included in this series. Involvement of the anterior uvea occurred in 48 cases, comprising prolapse or damage to the iris in 45 cases and ciliary body trauma in 24. With regard to the lens, in 39 cases there was a through-and-through injury, in 25 cases severe destruction, and in 7 cases a traumatic aphakia. Vitreous damage comprised prolapse in 41 eyes, and penetration of the vitreous substance in 31. Retinal injury of one form or another was evident in 40 cases; 27 showed direct retinal damage; 7 cases had a detachment present at the initial procedure, and contusional oedema or intraretinal haemorrhage was seen in a further 6. Altogether there was injury to 2 intraocular structures in 12 (17%) cases, 3 structures in 32 (44%), and 4 structures in 28 (39%) cases.

INDICATIONS FOR VITRECTOMY

On the basis of preoperative and operative assessment the perforating injuries included in this series underwent anterior segment debridement and vitrectomy. The decision to select out each case for vitrectomy was made on the basis of one or more of the following indications: (i) Injury of the lens with penetration or rupture of the posterior capsule and resulting vitreous/lens admixture; (ii) multistructure anterior segment injury with adherence of vitreous to damaged iris, ciliary body, lens, or cornea; (iii) perforating injury with vitreous haemorrhage and overt or suspected retinal damage; (iv) removal of a non-magnetic IOFB; (v) perforating injury with endophthalmitis. The frequency with which each situation was considered to be the main or subsidiary indication is shown in Table 3.

VISUAL RESULTS

The overall visual results based on the corrected visual acuity are shown in Table 4. The patients were divided into 4 groups in accordance with the WHO classification for designating visual impairment (Roy, 1974) to facilitate comparability with other statistics.

Table 3 *Indications for vitrectomy in 72 severely injured eyes*

	Main indication	*Subsidiary indication*
(i) Lens perforation	31	11
(ii) Anterior segment disruption	37	3
(iii) Vitreous haemorrhage	—	26
(iv) Non-magnetic IOFB removal	—	2
(v) Endophthalmitis	4	—

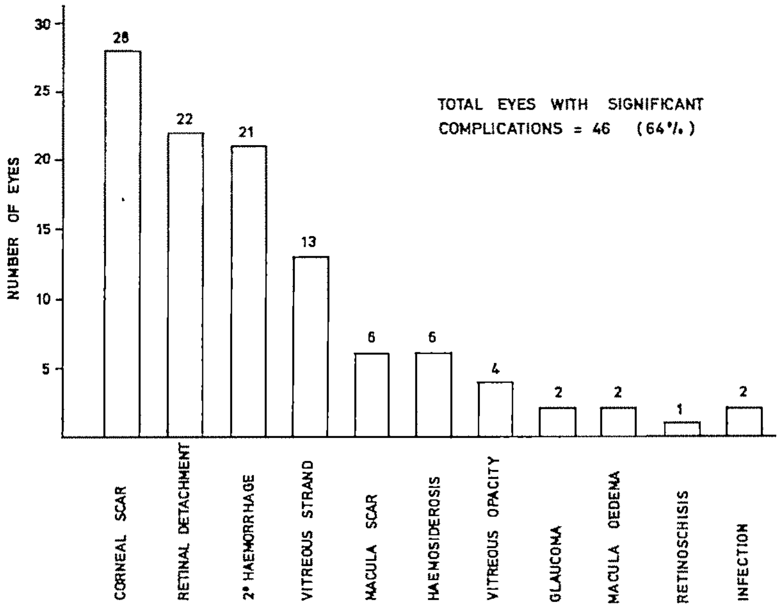

Fig. 4 *Incidence of complications*

Table 4 *Visual results in injured eyes after primary reconstruction*

Blind	$< \frac{6}{60}$	$\frac{6}{60} \rightarrow \frac{6}{18}$	$\frac{6}{12}$ *or better*	
19 (26%)	14 (19%)	18 (25%)	21 (30%)	– 72 – 100%

COMPLICATIONS

In compiling the incidence of complications shown in Fig. 4 only those have been included which developed or became evident during the post-operative period. Lesions present at the initial examination are regarded by several authors as immediate complications (Johnston, 1971) but for the purposes of this paper are considered as pre-operative or operative examination findings. The list of complications includes several categories of lesion. Injuries difficult or impossible to detect at the initial examination, such as macula damage, although clearly a direct consequence of the initial trauma, are legitimately included as complications only because of late discovery. Of greater concern in this study are complications such as vitreous strands, secondary haemorrhage, and retinal detachment, which develop as a result of the processes of regeneration and repair, and which begin within a few hours of the initial damage occurring (Coles and Haik, 1972). The objective of surgical treatment of injuries must be to reconstitute the structure of the injured eye, such that these processes progress purposefully and do not lead to the creation of further damage threatening ultimate visual recovery. The degree of success achieved in preventing or managing such complications is reflected in Figs. 5 and 6.

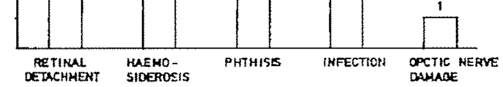

Fig. 5 *Causes of blindness*

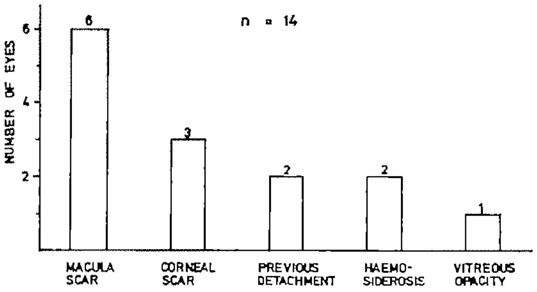

Fig. 6 *Causes of VA < 6/60*

RETINAL DETACHMENT

The largest single cause of blindness in eyes in this series was retinal detachment. Overall, this condition occurred in 27 eyes (37%), in 7 cases being recognised and treated at the time of primary surgery and in 22 cases developing subsequently. Successful reposition with one or more procedures was achieved in 18 eyes (66%). A retinal hole was found in 45% of cases. In the 22 secondary detachments traction due to vitreous strand (11) or post-haemorrhagic strand formation was a factor in 18 cases and massive periretinal proliferation in 3 cases.

SECONDARY HAEMORRHAGE

This complication occurred in 21 cases (29%), heralding a serious setback for the affected eye. The majority of episodes took place within a fortnight of injury, but in 2 cases 6 weeks elapsed. Analysis of the causes of blindness with reference to the effect of secondary haemorrhage is revealing. Thus, retinal detachment occurred in 57% of cases with haemorrhage and only 19% of cases without. The 4 cases of haemosiderosis were a direct result of haemorrhage, and it played a major role in the development of 3 phthisical eyes.

Exact data on the source of this haemorrhage were hard to obtain. Approached from the point of view of the tissues likely to bleed, the ciliary body might, on theoretical grounds, come under greatest suspicion. Ciliary body damage was indeed present in 50% of cases with secondary haemorrhage and only 21% of those without, but on this basis sclera could equally well be implicated. Injury to the iris appeared to be an occasional source, but retinal damage was statistically not significant.

Discussion

The results presented above have been obtained after treating a series of severe ocular injuries by methods which differ in important respects from more established conservative ones. In initiating this change to a more radical approach, the decision was made not to select out cases for inclusion in a control group, because the individual nature of each injury would make it impossible to determine at what point in the cases managed conservatively one should refrain from further surgical intervention. While the prime objective of this work was to assess the value of vitrectomy in severe injury therapy, it is clear that improved microsurgical instruments and techniques have also contributed to the results obtained.

More recently published series of the results of treating perforating injuries (Roper-Hall, 1959; Remky, 1965; Johnston, 1971) include many cases of a comparatively minor nature, making comparison difficult. Lens damage occurred in only 41% of the Munich severe cases and 31% of the Birmingham group. Nevertheless, the fact that the visual results in Table 3 break down into a pattern broadly similar to that in other series indicates that severe injuries do better visually after radical reparative procedures, a contention supported by Heimann (1972) and confirmed by a closer study of earlier statistics. In Johnston's series of 295 cases, of the 54 eyes with traumatic cataract and vitreous loss only 5 (9%) recovered a visual acuity of 6/12 or better, compared with 30% in this study.

Figs. 5 and 6 show that of the eyes blind or with vision less than 6/60 only a small proportion resulted from primary tissue damage, the majority becoming irreparably damaged as a consequence of complications. Comparison with complications encountered in other series shows striking differences in incidence and severity. Cataract as a major cause of visual impairment is eliminated (cf. Johnston, 1971). Glaucoma occurred in less than 1% of cases compared with 10% (Johnston, 1971; Watz and Reim, 1973). Chronic non-infective uveitis was not encountered. Retinal detachment, however, occurred in 30% of cases, as one would expect with such injuries. The results of detachment surgery are comparable to the figures of Klöti (1972).

The high incidence of detachment developing as a secondary complication is disturbing. The role of vitreous destruction in the pathogenesis of detachment after perforating injuries was stressed by Witmer (1972). In this series it was intended to reduce the likelihood of traction detachment by avoiding incarceration of vitreous and preventing adherence to damaged structures with a fibroblastic potential. Any benefit radical debridement and vitrectomy may have conferred would appear to be much reduced by the effect of secondary haemorrhage, whose significance in detachment is well documented (Percival, 1972).

The possibility must be considered that early radical surgery predisposes to secondary intraocular haemorrhage, and it may be that major reconstructive procedures should be delayed for a period of time until the ocular condition stabilises (Machemer, 1976; Benson and Machemer, 1976; Hutton *et al.*, 1976).

When the cases of haemosiderosis and phthisis are taken into consideration, 70% of the blind or enucleated eyes (Fig. 5) resulted from, or were associated with, severe secondary haemorrhage, which has emerged as the major problem being encountered.

Future efforts to improve the prognosis in severely injured eyes (managed along these lines) will therefore need to be directed at dealing more effectively with haemorrhage, either by removal, by promoting more rapid absorption, by chemical alteration to a harmless form, or preferably by finding and eliminating the source.

The quantities of blood which can be released into the vitreous cavity before causing significant retinal toxicity have been studied in monkeys (Sanders *et al.*, 1975). Vitreous cavity lavage as a method, albeit relatively crude, of reducing amounts of intraocular haemorrhage to levels which can be tolerated and effectively dealt with by the eye's own reparative mechanisms is at present under study at the Freiburg clinic.

We thank Professor Dr G. Mackensen for his guidance in the management of cases included in this study and for his help and encouragement in the preparation of this paper. We are grateful to Frau Kukula for the diagrams.

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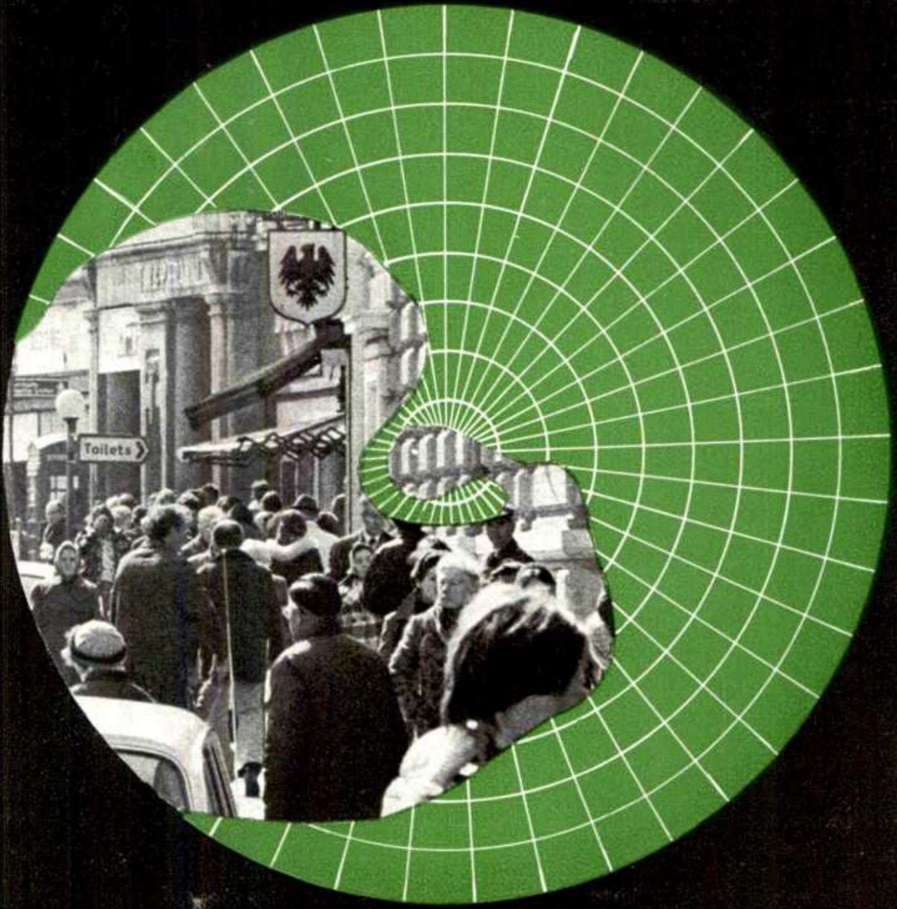

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Vitrectomy technique in anterior segment surgery

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SUMMARY Instruments designed primarily for vitreous surgery were used in 74 anterior segment operations. In each case the instrument was introduced into the eye through a limbal incision. This preliminary report shows that this new approach offers several advantages over conventional methods in selected cases. It is of particular value in the management of presenile and complicated cataracts and in the removal of capsulo-lenticular remnants and pupillary membranes. A larger number of cases and longer follow-up are necessary to define further the specific indications and limitations of this technique.

The recent development of instruments that will cut and remove ocular tissue through a very small incision represents a significant departure from conventional ophthalmic surgical procedures. Most instruments consist of 2 metallic tubes (Machemer *et al.*, 1971; Peyman and Dodich, 1971; O'Malley and Heintz, 1972; Douvas, 1973; Kloti, 1973; Federman *et al.*, 1974). Tissue aspirated into the tip of the outer tube is cut by a shearing action produced by the rotation or oscillation of the inner tube. Evacuation is performed by suction from an aspirating syringe that draws the tissue into the inlet and removes it from the eye. The inflow of fluid is controlled by gravity. The instrument can be introduced into the eye through an incision at the limbus or pars plana.

The purpose of this report is to present a preliminary analysis of our experience in anterior segment surgery using instruments containing infusion, aspiration, and cutting features as designed for vitreous surgery.

Patients and methods

During 13-months' period (January 1976 to January 1977), 74 anterior segment operations were performed with a vitrectomy instrument; 53 were performed with the Kloti vitreous stripper and 21 with the Keeler-Federman SITE. The patients (31 females and 60 males) ranged in age from 6 months to 63 years. 8 patients had both eyes operated on at different times, and a further patient had 2 operations on 1 eye and 1 operation on the other eye.

Ocular evaluation included best corrected visual acuity, external slit-lamp biomicroscopy, applanation tonometry, and ultrasonography in selected cases. Pre- and postoperative anterior segment photographs were obtained when possible.

Patients were usually admitted to hospital 1 or 2 days before the operation and remained 4 to 7 days after it. 71 operations were performed under general anaesthetic, 2 under neuroleptic anaesthetic, and 1 under local anaesthetic. After the completion of surgery all eyes were given a subconjunctival injection of gentamicin and betamethasone. Mydriatic and antibiotic-steroid drops were instilled frequently after operation. After discharge, patients were followed up at 2- to 4-weekly intervals until a stable state had been reached.

Of the 54 eyes that underwent lensectomy 35 had cataracts due to chronic anterior uveitis; extensive posterior synechiae were present in the majority of these eyes. Of the 6 eyes with congenital cataracts 2 were thought to have been due to maternal rubella. Of the 9 eyes with traumatic cataracts 5 had suffered penetrating injuries and 4 blunt trauma. There were 3 eyes with presenile cataracts, and one 63-year-old patient with a posterior subcapsular cataract underwent lensectomy during a combined lensectomy-vitrectomy procedure.

Of the 16 eyes that had anterior segment reconstruction for the removal of capsulo-lenticular remnants, pupillary membranes, or pupil enlargement, 2 had had previous surgery for traumatic cataracts, 5 for congenital cataracts, and 9 for complicated cataracts due to chronic anterior uveitis. In 4 eyes a traumatically subluxated lens was removed.

Operative technique

A wire lid speculum is inserted and the eye is steadied

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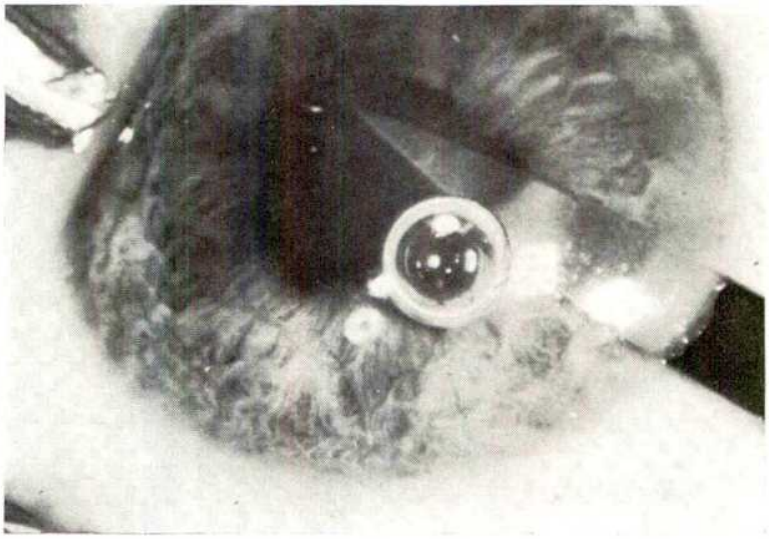

Fig. 1 *Lensectomy of cataract secondary to chronic anterior uveitis. An oblique stab incision is made with a Graefe knife at 10 o'clock just inside the limbus. The knife is then passed into the lens nucleus*

with fixation forceps; traction sutures are not required. An oblique incision at 10 o'clock just inside the limbus is made with a Graefe knife (Fig. 1). The hardness of the lens nucleus is then tested. If the knife does not penetrate the nucleus easily, an alternative method of extraction has to be used. It is important to avoid damaging the posterior capsule at this stage and not to dislocate the lens by probing too forcibly at a hard nucleus. If the cataract is suitable for lensectomy the corneal incision is enlarged. An overtight incision may leak postoperatively owing to stretching of the corneal tissues, and too large an incision will leak during the operation.

After the instrument is introduced into the eye (Fig. 2) as much lens matter as possible is removed working within the capsular bag (Fig. 3). This minimises excessive irrigation of the corneal endothelium. The assistant should wait until he sees the tip of the instrument applied to the lens matter and then aspirate fairly forcibly so as to engage it into the aspiration port (Fig. 4). Sometimes the lens fibres will not aspirate immediately, but if suction is maintained for a few moments they

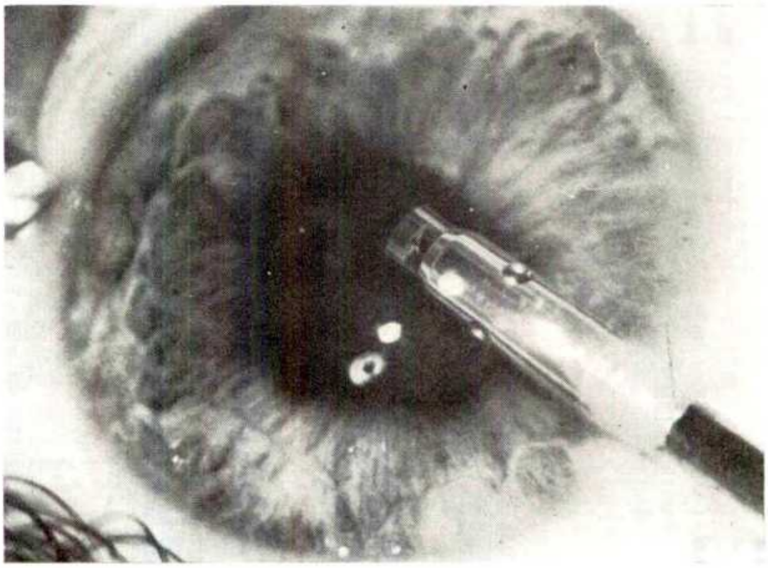

Fig. 2 *The incision is slightly enlarged and the vitrectomy instrument is introduced into the anterior chamber along the track made by the knife*

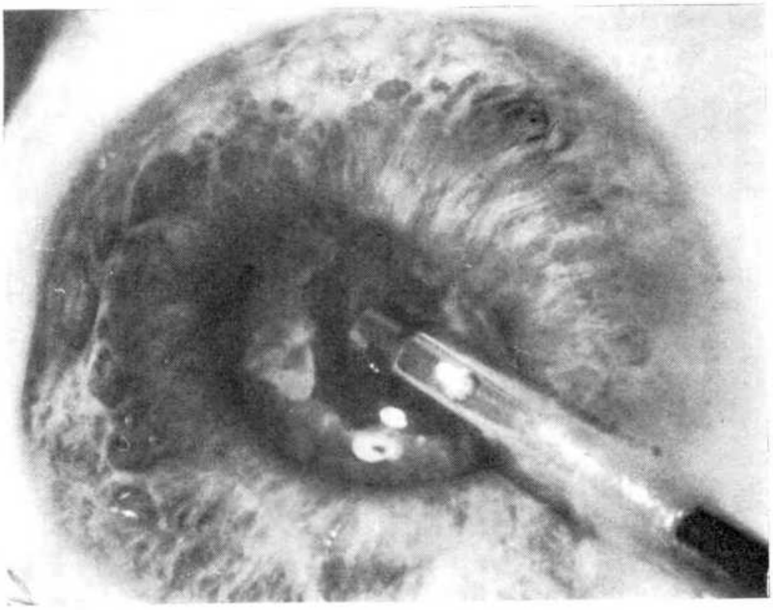

Fig. 3 *Lensectomy is commenced by aspiration and cutting*

deform and then aspirate quite suddenly. When this occurs the assistant should stop aspirating so as not to collapse the anterior chamber. Anterior chamber collapse can be avoided quite easily, and computer-controlled infusion and aspiration does not appear to be necessary. As much soft lens matter as possible is removed in this way without operating the cutting mechanism, though cutting will speed up the process and is necessary for harder lens material and also for capsule, cyclitic membranes, iris, and vitreous.

After as much lens matter as possible has been aspirated the anterior capsule is removed and, if necessary, the pupil enlarged. The remaining lens matter is then dislocated from within the capsular bag and drawn into the centre of the pupil or into the anterior chamber. The posterior and peripheral layers of the lens can be peeled away from the

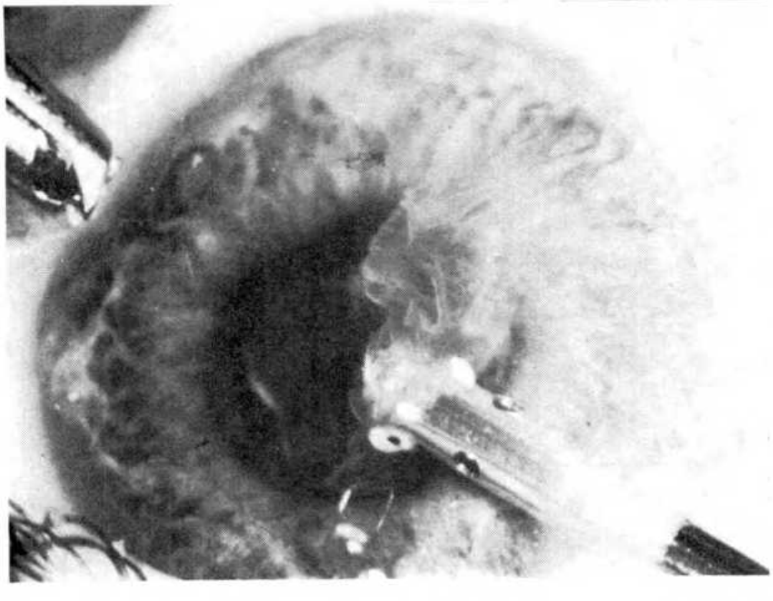

Fig. 4 *Lensectomy is nearing completion. The posterior capsule is still intact in order to prevent lens material from falling into the vitreous cavity*

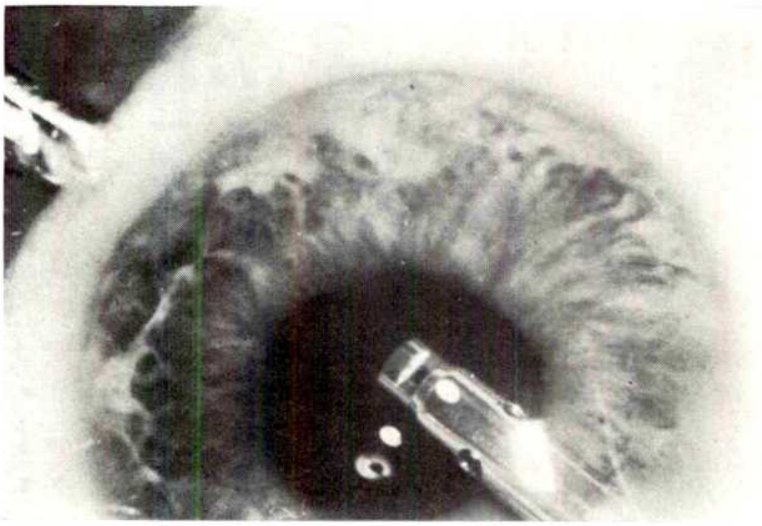

Fig. 5 *Eye after completion of lensectomy and removal of posterior capsule*

posterior capsule. Allowing the anterior chamber to collapse slightly at this stage helps to express lens matter from under the iris into the centre of the pupil. It is important to avoid aspirating the vitreous base so as not to cause traction and subsequent retinal dialysis. Finally, the posterior capsule is removed and a shallow anterior vitrectomy performed. It is important to remove the posterior capsule in eyes with chronic iridocyclitis so as to prevent the formation of postoperative membranes. In eyes with congenital cataracts it is possible to leave the posterior capsule behind. The instrument is then removed from the eye (Fig. 5) and air injected into the anterior chamber. The bubble should extend as far as the internal opening of the incision so as to prevent the formation of anterior synechiae. No sutures are necessary unless the incision has inadvertently been made too vertical or the air is not retained.

Bleeding during the operation from the iris or vascularised membranes usually stops spontaneously; occasionally it may be necessary to cauterise the bleeding point (Fig. 6).

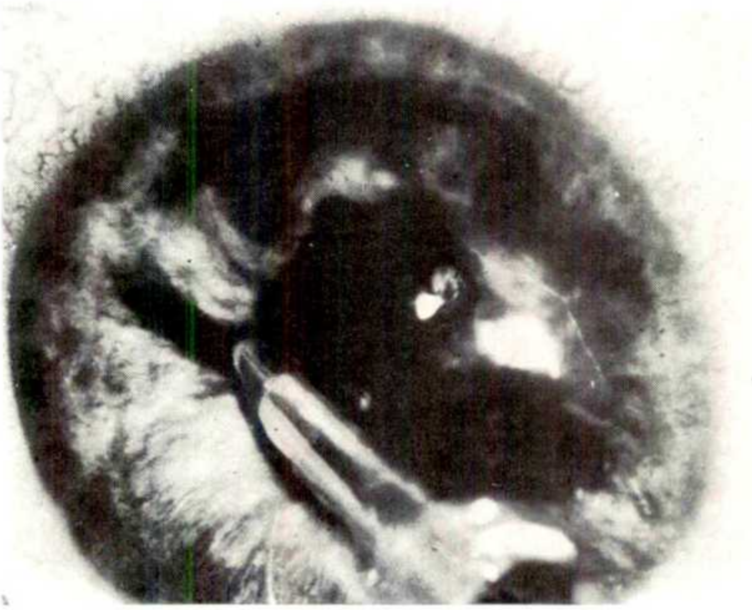

Fig. 6 *Cauterisation of bleeding iris vessels*

Results

Lensectomy (54 eyes)

Accurate assessment in visual acuity was possible in 45 eyes. It can be seen from Table 1 that in 40 eyes (89%) the preoperative visual acuity was 'counting fingers' or less, and the postoperative visual acuity of 6/12 or better was achieved in 17 eyes (38%). 36 eyes had an improvement in visual acuity, in 7 eyes there was no change owing to pre-existing lesions (retinal detachment in 2 and gross field loss in 1), and 2 eyes developed retinal detachment postoperatively.

In 3 eyes the lensectomy failed as the lens was calcified. The section was enlarged and the cataract was removed with a cryoprobe. In another eye only a partial lensectomy was possible owing to unexpected hardness of the lens. Fortunately, the remaining lens material absorbed spontaneously during the next 8 weeks.

In 6 eyes there was loss of lens material into the vitreous cavity during the operation. In 4 eyes the amount of lens material was very small and in each case it absorbed spontaneously. In 2 eyes the whole nucleus was lost. An unsuccessful attempt to retrieve it was made in 1 eye with the vitrectomy instrument. This resulted in the formation of a retinal tear and subsequent inoperable retinal detachment. The nucleus was later removed from the anterior chamber with the cryoprobe. In another eye a retinal detachment formed 6 weeks after an uneventful lensectomy. It is thought that this was the result of excessive traction on the vitreous base by the vitrectomy instrument resulting in the formation of a dialysis.

Transient striate keratitis occurred in 5 eyes. In each case this followed prolonged manipulation of lens material in the anterior chamber of eyes with relatively hard nuclei. It seems probable that this resulted in endothelial damage.

Reoperation was necessary in only 1 eye. This was to remove a pupillary membrane which was the result of postoperative bleeding. A bleeding disorder was suspected in this patient. A summary of the complications is listed in Table 2.

Table 1 *Visual acuity in 54 eyes before and after lensectomy*

Visual acuity	*No. of eyes*	
	Preoperative	*Postoperative*
6/12 or better	0	17
6/18–6/24	3	7
6/36–6/60	2	7
Counting fingers	11	3
Hand movements	13	5
Light perception	16	6
Too young to measure	9	9
Total	54	54

Table 2 *Complications of lensectomy in 54 eyes*

	No. of eyes
Surgical complications:	
Partial lens removal	1
Loss of lens nucleus into vitreous	2
Postoperative complications:	
Transient striate keratitis	5
Formation of pupillary membrane	1
Retinal detachment	2

On the whole, eyes with chronic uveitis tolerated lensectomy very well, with no significant reactivation of uveitis during the postoperative period despite the fact that over 60% of eyes had active inflammation at the time of surgery.

Anterior segment reconstruction (16 eyes)

Successful removal of capsulo-lenticular remnants (Fig. 7*a*, *b*), pupillary membranes, and pupillary

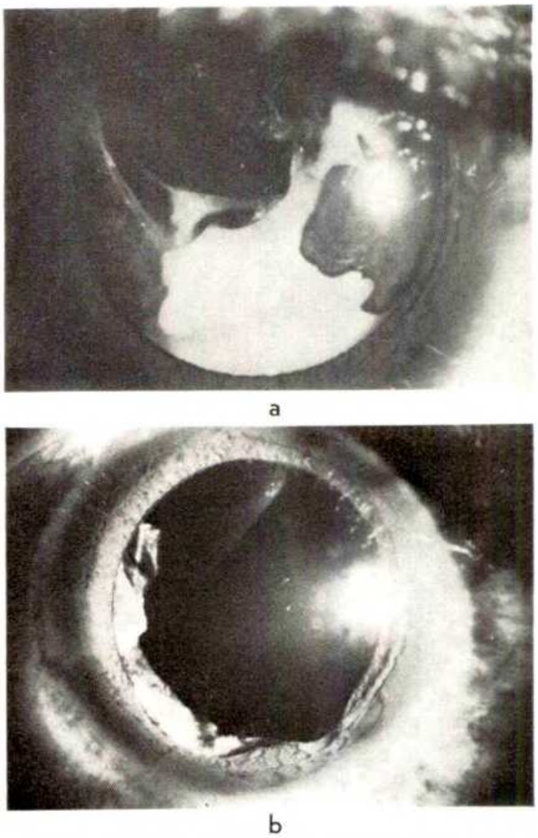

Fig. 7 (a) *Capsulo-lenticular remnants after conventional congenital cataract surgery.* (b) *Appearance after operation with vitrectomy instrument*

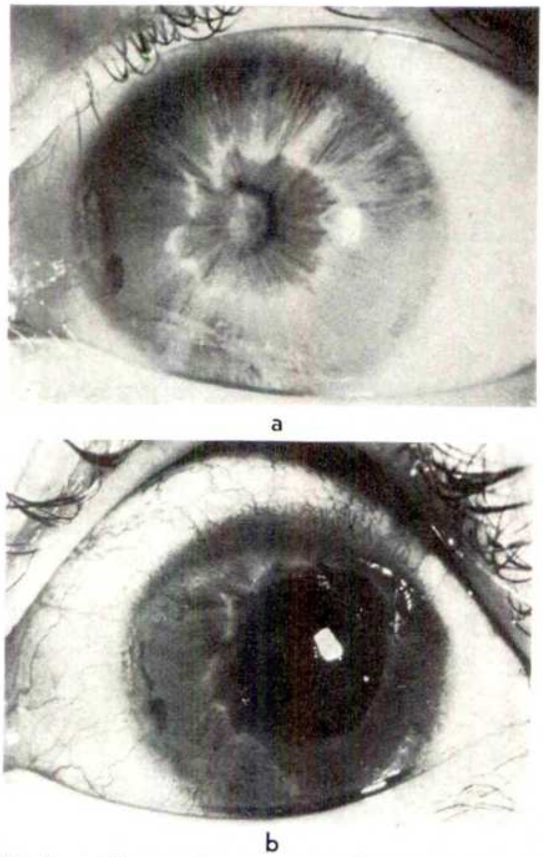

Fig. 8 (a) *Preoperative appearance of cataract secondary to chronic anterior uveitis.* (b) *Postoperative appearance*

enlargement with the vitrectomy instrument was achieved in 14 eyes. In 1 eye with a very tough post-traumatic membrane, a two-instrument technique using Vanas scissors was necessary in order to achieve a pupillary opening. In another eye with a suspected persistent hyperplastic primary vitreous it was impossible to obtain an opening.

Although in the majority of eyes visual improvement was slight owing to pre-existing retinal damage, no serious complications resulted.

Removal of subluxated lens (14 eyes)
A traumatically subluxated cataractous lens was successfully removed in 4 eyes. A preliminary anterior vitrectomy was performed, the incision was enlarged, and the lens was extracted with the cryoprobe.

Discussion

On the whole the results of the vitrectomy technique in anterior segment surgery have been encouraging and in selected cases appear to be an improvement on conventional methods.

Lensectomy has several advantages over conventional intracapsular cataract extraction. The small limbal incision, which frequently does not require to be sutured, allows early ambulation and discharge of the patient from hospital. It is now becoming apparent, however, that with present-day suturing methods this is also possible with standard intracapsular extraction (Galin *et al.*, 1974). The amount of surgically induced astigmatism is small, and patients can be fitted with their final correction earlier. The incidence of vitreous loss is negligible. Should vitreous herniate into the anterior chamber it can readily be removed with the vitrectomy instrument. This is particularly useful in the removal of subluxated lenses. If the lens is too hard for lensectomy then it is possible to do a preliminary anterior vitrectomy, enlarge the corneal incision, and then remove the lens with the cryoprobe.

Lensectomy also has some advantages over phacoemulsification. It is a cheaper and easier technique, which does not require a deep anterior chamber or a large pupil. The posterior capsule can be removed during the initial operation and a subsequent capsulotomy is not required. The main limitation of lensectomy is that it is not, as yet, a suitable technique for the removal of hard cataracts. Although it is possible to remove posterior subcapsular cataracts in elderly patients, who do not have significant nuclear sclerosis, this usually necessitates prolonged manipulation of lens material in the anterior chamber, which increases the risks of endothelial damage and subsequent corneal oedema. Nearly all our severe complications (corneal oedema in 5 eyes and loss of the lens nucleus into the vitreous cavity in 2 eyes) were the direct result of underestimating the hardness of the lens. It is hoped that with more experience with this technique the incidence of these complications will be reduced.

For soft uncomplicated cataracts in children lensectomy is a very good alternative to aspiration. It offers the additional advantage of not requiring a separate infusion system. It also enables a more controlled procedure to be carried out with a more complete removal of cortical lens matter and capsule.

Lensectomy has a significant advantage over aspiration in the management of cataracts secondary to chronic anterior uveitis. These eyes invariably have small pupils with extensive posterior synechiae (Fig. 8*a*), making access to the lens very difficult. With the vitrectomy instrument the pupil can be enlarged and all adhesions can be freed prior to lensectomy (Fig. 8*b*). Another advantage of lensectomy is for the removal of cataracts in patients between the ages of 30 and 40 years, who are too

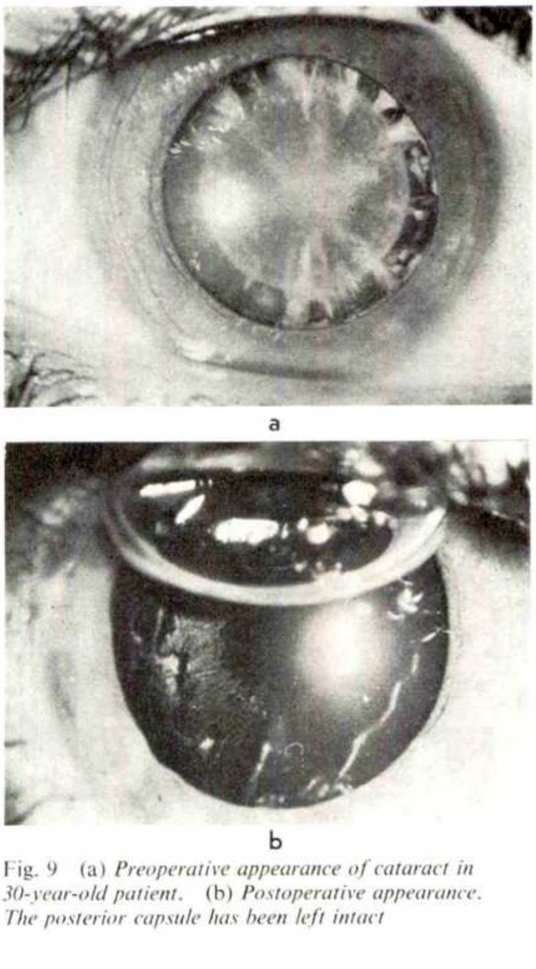

Fig. 9 (a) *Preoperative appearance of cataract in 30-year-old patient.* (b) *Postoperative appearance. The posterior capsule has been left intact*

old for the nucleus to be aspirated but have a high risk of vitreous loss with conventional intracapsular extraction (Fig. 9*a*, *b*).

The vitrectomy technique is very useful in anterior segment reconstruction. Some have advocated a pars plana approach (Peyman and Swartz, 1975) to these problems. We feel that, although the pars plana approach may be used in certain cases, we generally prefer to introduce the instrument through a limbal incision so as to avoid the possibility of inducing retinal dialyses. Should a tough membrane be treated with the two-instrument technique then a pars plana approach may be indicated so as to spare the endothelium from prolonged exposure to the infusion stream.

We acknowledge the help and encouragement of Mr J. R. Hudson, and the surgeons and house surgeons of Moorfields Eye Hospital, High Holborn.

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Immunoglobulins in human aqueous humour

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SUMMARY The immunoglobulin concentrations in human aqueous humour from 44 patients aged 35 to 85 years with cataracts were measured by a standard immunodiffusion method. IgG was found in all the samples (mean level 7·0 mg/100 ml). IgD, IgA or IgM could not be detected. There was no significant difference in IgG levels in aqueous humour between the two sexes, in different age groups, and in the different types of cataracts.

The immunoglobulin content in internal secretions such as cerebrospinal fluid, aqueous humour, and synovial fluid differs from that in external secretions such as tears, saliva, nasal and bronchial fluids, colostrum, breast milk, perspiration, and jejunal juice (McClellan *et al.*, 1973; Tomasi and Bienenstock, 1968). Though considerable data have recently been collected on the immunoglobulin level in human tears (Sen *et al.*, 1976), very little work has been done to establish the level in the aqueous humour of human eyes. Difficulties are obvious in obtaining samples from living absolutely normal human eyes. On the other hand the validity of the results of necropsy studies on the composition of immunoglobulins in aqueous is in doubt, as it is known that the composition of aqueous changes rapidly after death (Hemmingsen and Øther, 1967; Dieckhues, 1967; Allansmith *et al.*, 1973).

It was therefore decided to study the immunoglobulin levels in aqueous humour in living eyes with senile cataractous changes so that the available data could be used as control for further studies in various ocular diseases.

Subjects and methods

44 cases with cataractous changes were included in the study. All of them reported to Irwin Hospital for extraction of the lens. The mean age of these patients was 55·9 years (SD 10·0, range 35 to 85 years). There were 21 females with mean age 54·3 years (SD 8·8, range 40 to 70 years), and 23 males with mean age 60·0 years (SD 10·8, range 35 to 85 years). 14 cases showed early senile cataractous changes, 13 moderate senile cataractous changes, and 17 nearly mature senile cataracts. Hypermature cataracts were excluded from this study, as it was feared that some of them might have unsuspected minimal leakage of lens matter into the aqueous. All the cases were otherwise healthy both systemically and on local examination, including slit-lamp biomicroscopy. When the posterior segment could not be examined preoperatively owing to the presence of advanced cataractous changes, it was examined after operation to rule out any lesion.

Samples of aqueous humour were collected from the eyes just before the extraction of the lens under local anaesthesia, care being taken not to contaminate aqueous with blood. A small stab incision was made with a keratome at the limbus, and aqueous humour was drawn into a tuberculin syringe fitted with a fine cannula. The total quantity of sample obtained was 200 μl approximately. The samples were stored in screw-capped vials at −20°C until needed. The IgA, IgG, IgD, and IgM in the samples were measured by a single radial immunodiffusion method (Mancini *et al.*, 1965) using monospecific goat antisera against heavy chain human IgA, IgG, IgD, and IgM. The respective reference standards, except that of IgA, were obtained from Meloy Laboratories, USA. The reference standard of secretory IgA was prepared from human colostrum.

Antihuman lambda and anti-human kappa antisera (Meloy Laboratories) were used to detect lambda and kappa light chains in the aqueous humour. The IgG was characterised against anti-gamma chain (WHO), anti-Fc, and anti-Fab (Nordic, Denmark) antisera. Human myeloma IgG (λ) obtained from Meloy Laboratories served as control.

Results

IgG was invariably found in all the samples. The mean level was 7·0±4·2 mg/100ml (range 1·5 to

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17·6 mg/100 ml). There was no significant difference statistically (P < 0·10) between the IgG level in the males (6·5, SD 4·6 mg/100 ml, range 1·5 to 17·6 mg/100 ml) and that in the females (7·6, SD 4·2 mg/100 ml, range 2·4 to 17·0 mg/100 ml), though the level in females tended to be higher. The distribution of IgG level in different age groups is given in Table 1. There was no statistically significant difference in the IgG level between the various age groups. The distribution of IgG level in different types of cataracts is given in Table 2. There was also no significant difference statistically in the IgG level in aqueous humour in different types of cataracts. IgA, IgM, or IgD were not detected in any of the aqueous samples.

The study of the distribution of the types of light chains among the IgG molecules present in the aqueous shows that they had predominantly lambda chains. Thus lambda chains were detected in 80% of samples, kappa chains in 8% of samples, and both chains in 8% of samples.

The IgG in aqueous has been characterised by various monospecific antisera. It gave sharp precipitin lines with anti-gamma chain and anti-Fc and anti-Fab antisera. Myeloma-IgG (λ), which served as control, also gave precipitin lines with these three antisera. It is therefore concluded that IgG molecules in aqueous have intact heavy and light chains. The latter is predominantly of the lambda type.

Discussion

IgG is the predominant immunoglobulin in the internal secretions, the ratio of IgG to IgA being 5:1 approximately, with a smaller proportion of IgM (McClellan *et al.*, 1973). However, data on the immunoglobulin level in living human eyes are scanty. Audain *et al.* (1974) studied the immunoglobulin content of human aqueous from 5 senile cataractous eyes. They found IgG levels in all the samples, the values ranging from 5 to 8·5 mg/100 ml. IgA levels in two samples were 4 and 4·5 mg/100 ml (absent in three other cataract cases), and they failed to detect IgM and IgD in any sample. The normal average concentrations of immunoglobulins in the human aqueous as determined by Schmut and Zirm (1974) were IgG 13·6 mg/100 ml, IgA 4·0 mg/100 ml, and IgM 3·9 mg/100 ml. They reported IgM in 40% of the cases. In our series of samples from cataractous eyes the only immunoglobulin that could be detected was IgG, the level being 7·0 mg/100 ml and range 1·5 to 17·6mg/100ml.

Table 1 *IgG level in mg/100 ml in the aqueous humour of cataract cases in different age groups*

Age group in years	*No. of cases*	*IgG Mean ± SD*	*Coefficient of variation in percentage*	*Range*
35–44	7	8·2 ± 4·5	54·8	2·4–17·0
45–54	11	5·4 ± 2·5	46·3	1·5–11·0
55–64	18	7·1 ± 3·2	45·0	2·4–15·0
65 and above	8	7·8 ± 5·2	66·6	1·5–17·6

Table 2 *IgG level in mg/100 ml in the aqueous humour of cataract cases in different types of cataracts*

Cataract type	*No. of cases*	*IgG Mean ± SD*	*Coefficient of variation in percentage*	*Range*
Early senile changes	14	6·5 ± 4·3	66·1	1·5–17·6
Moderately advanced senile changes	13	7·8 ± 5·2	66·6	1·5–17·0
Mature senile cataract	17	6·0 ± 3·1	51·6	2·4–16·0

Zirm and Schmut (1973) found a significant increase in concentration of immunoglobulin during ageing but no obvious sex-related difference. Our data show that there is no significant difference in IgG level in aqueous in cataractous eyes in the different age groups studied and in various types of cataracts.

We thank Dr R. Thompson, Birmingham, England, for his gift of human colostral IgA standard, and Dr G. Torrigiana, of the World Health Organisation, Geneva, Switzerland, for giving us various anti-human immunoglobulin antisera, their reference standard, and myeloma serum.

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Immunoglobulins in tears in trachoma patients

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SUMMARY Tear immunoglobulin concentrations have been measured in 100 healthy people and 62 patients in different stages of trachoma. In healthy people the average IgA level was 27·8 mg/100 ml. There was no significant difference in the IgA level in various age groups and between the sexes. IgG was detected in 92 samples, and it was less than 1 mg/100 ml. IgM in tears was detected in only one sample. IgD was not detected in any specimen. In trachoma cases, the mean IgA level was found to be significantly lower (22·0 mg/100 ml) than in healthy people. There was no significant difference in IgA level between different stages of trachoma. IgG, IgD, and IgM could not be detected in any sample from the trachoma cases.

The pathogenesis of trachoma, a localised chronic disease of the eye, is not yet properly understood. Silverstein (1973) suggested that immunoglobulins may play some role. The immune components of trachoma are suggested by the prolonged follicular hypertrophy seen clinically and the dense infiltration of the conjunctiva by lymphocytes, plasma cells, and macrophages. Since plasma cells produce immunoglobulin, the tear immunoglobulin concentration may be altered in trachoma (McClellan *et al.*, 1974).

The main objective of the present study was to find out whether the tear immunoglobulin level alters in trachoma patients.

Patients and methods

The study was carried out among 62 trachoma patients and 100 healthy people chosen consecutively from the Eye Outpatient Department of Irwin Hospital, New Delhi, during the period from February to August 1976. The latter group comprised persons who had no evidence of ocular or systemic disease and who had attended mainly for the purpose of refraction.

An earlier report by the present authors has already described the IgA level among healthy Indian people (Sen *et al.*, 1976). However, for the purpose of the present investigation it was considered advisable to examine a fresh group of healthy persons to serve as concurrent controls for the study of trachomatous patients. Human tear specimens were collected by the technique as described previously (Sen *et al.*, 1976). The details of the cases are given in Table 1.

The sex ratio in the 2 groups (normal and trachoma) was almost the same. As for age, there was a slight difference between the 2 groups but, on the whole, it was not of a magnitude to warrant age standardisation of results. The trachoma stages were determined by clinical examination with the help of slit-lamp biomicroscopy by one of us (D.K.S.). The diagnosis was made in accordance with MacCallan's classification (MacCallan, 1913) as modified by the standards of World Health Organisation (WHO, 1962). The samples were stored at -20°C until needed. IgA, IgG, IgD, and IgM were quantified by a single radial immunodiffusion method (Mancini *et al.*, 1965). Mono-

Table 1 *Age and sex distribution of normal and trachoma patients included in the study*

	Normal persons		*Trachoma patients*					
			I	*II*	*III*	*IV*	*All stages*	
	No.	*%*					*No.*	*%*
Males	55	55·0	9	5	10	5	29	46·8
Females	45	45·0	9	8	9	7	33	53·2
Age in years								
0	4	4·0	—	—	—	—	—	0·0
5	7	7·0	1	1	1	—	3	4·8
15	44	44·0	15	11	5	4	35	56·4
35	14	14·0	2	—	3	11	16	9·7
45+	31	31·0	—	1	10	7	18	29·0
Total	100	100·0	18	13	19	12	62	100·0

Address for reprints: Dr D. K. Sen, Department of Ophthalmology, Maulana Azad Medical College and Irwin Hospital, New Delhi-110002, India specific goat antisera against heavy chain human IgA, IgG, IgD, and IgM and the respective reference standards except that of IgA were obtained from Meloy Laboratories, Virginia, USA. The reference standard of secretory IgA purified from human colostrum was used.

Results

NORMAL CONTROLS

IgA was found in all the samples, the average being 27·8±15·3 mg/100 ml. Its level in females (mean 30·1±16·4 mg/100 ml) was somewhat higher than in males (mean 25·8±14·4 mg/100 ml), but the difference does not attain statistical significance (0·10<P<0·20). Statistical analysis was carried out to determine if there was any correlation between age and IgA level. It was found that r=0·12, P>0·10, suggesting that there is no statistically significant correlation between the two. IgG was detected only in 92 samples and the concentration was less than 1 mg/100 ml in every instance. IgM was not detected in any of the samples except one, in which case it was less than 1 mg/100 ml. IgD was not detected in any sample

TRACHOMA CASES

Here again IgA was found in all the samples, the average being 22·0±12·1 mg/100 ml. The mean level in successive stages of trachoma was 23·4, 23·1, 19·7, and 22·3 mg/100 ml respectively. The IgA level in different stages of trachoma and in healthy subjects is shown in Table 2.

Before attempting a comparison between the healthy people and the trachoma patients it is essential to ensure its validity. Apart from the randomness of the 2 samples (obtained by including healthy people and patients consecutively) there appear to be two more prerequisites for such a comparison, namely (1) that the 2 groups are similar in such respects as age and sex, and (2) that the trachoma patients, comprising, as they do, cases at different stages of the disease, are not a heterogeneous group. As to the first of these, it may be noted that the 2 groups are almost similar except for some slight differences in the age distribution. However, as we have seen, age does not appear to have any relationship with IgA level, and the minor differences in age distribution can be safely ignored. As to the second point, it is useful to compare the IgA level among patients at different stages of the disease. For this purpose an analysis of variance was carried out and the results are given in Table 3.

Table 2 *IgA level in mg/100 ml in healthy subjects and trachoma patients*

	No. of cases	*Mean ± SD*
Normal control	*100*	*27·8 ± 15·3*
Trachoma cases		
Stage I	18	23·4 ± 11·0
Stage II	13	23·1 ± 13·2
Stage III	19	19·7 ± 12·6
Stage IV	12	22·3 ± 12·6
All stages	62	22·0 ± 12·1

Table 3 *Analysis of variance*

Source of variation	*DF*	*Total sum of squares*	*Mean sum of squares*
Between the trachoma stages	3	150	50·0
Within the trachoma stages	58	8,771	151·2
Total	61	8,921	—

Between ss < within ss, hence formal test of significance unnecessary

It is clear that patients in various stages of trachoma do not differ significantly from each other in so far as the IgA level is concerned. It is therefore in order to combine them for a comparison with the healthy group of persons. As stated earlier, the mean IgA level among 62 trachoma patients was 22·0 compared to 27·8 among the 100 normals. This difference is statistically significant (P<0·05).

Discussion

Chandler *et al.* (1974) found that the concentration of IgA in tears remained remarkably constant despite the presence or absence of disease. Maythar and Zakay-Rones (1972) estimated the concentration of IgA and IgG in tears from normal individuals and trachoma patients and found no significant changes in the 2 groups. McClellan and others (1974) found IgA and IgG levels in children with trachoma to be lower than in normal persons and the difference was statistically significant. Bluestone *et al.* (1975) have reported that IgG is usually detectable but only occasionally quantifiable in tears from normal and diseased eyes. In our series we found lower IgA levels in cases with trachoma than in healthy persons and the difference was highly significant statistically. We also found IgG to be detectable, though not quantifiable, in 92 out of 100 healthy persons but undetectable in all trachoma cases.

It is difficult to understand why an infected group should have a lower immunoglobulin level. It has been postulated that the low level of immunoglobulin in tears from trachoma patients may be due to the inflammation in the upper fornix, which partially occludes the opening of the lachrymal tubules and prevents stimulation of the lachrymal gland plasma cells or interferes with the flow of tears down the tubules (McClellan *et al.*, 1974). Another suggestion is that the immunoglobulin deficiency in persons suffering from trachoma is inherent, which makes them prone to infection by trachoma agents. We are inclined to think this is more plausible. It has been suggested that immunoglobulin in tears provides the body with a first line of defence against invasion by micro-organisms. South *et al.* (1968) showed that immunoglobulin-deficient children were subject to recurrent conjunctivitis. Kaufman (1969) has reported a superficial keratitis among patients with hypogammaglobulinaemia who had no demonstrable IgA in their tears.

We acknowledge with thanks the help in statistical analysis by Mr G. P. Mathur, statistician, New Delhi Tuberculosis Centre, New Delhi. Thanks are due to Dr R. Thompson, Birmingham, England, for donated purified colostral standard.

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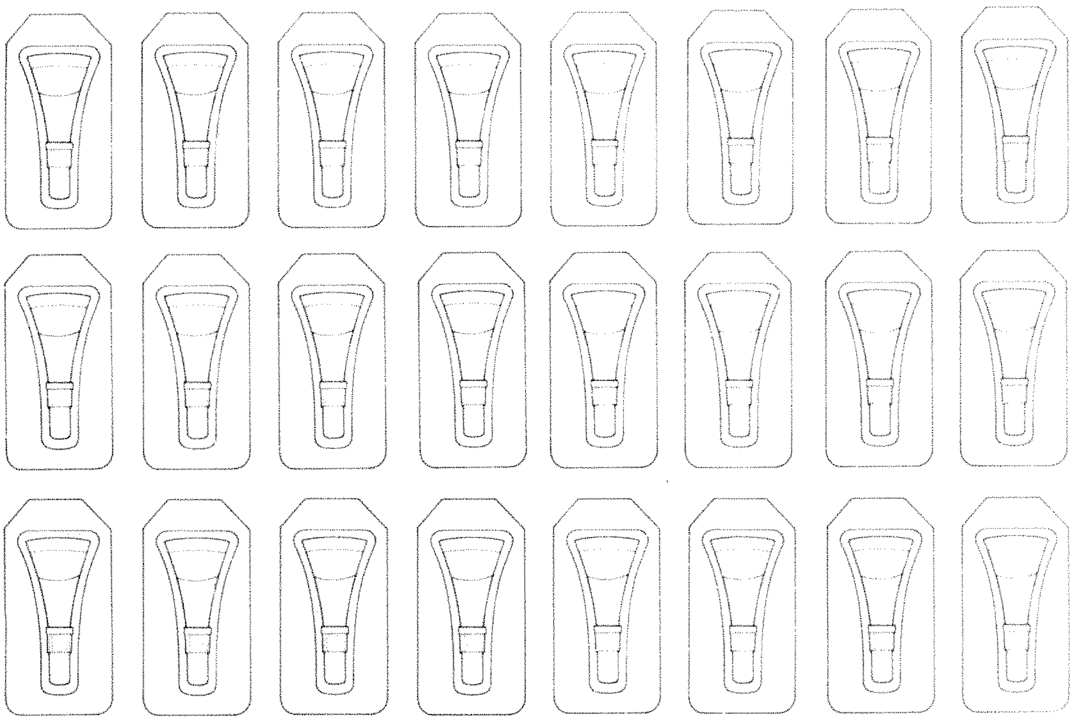

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Histopathological changes in malignant melanomas of the choroid after cobalt plaque therapy

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SUMMARY A series of 23 eyes removed after cobalt plaque therapy for malignant melanoma of the choroid is presented, and the histological changes are described with particular reference to the presence or absence of necrosis in the tumours. In 17 of the 23 eyes no evidence of tumour necrosis was found, though all showed evidence of radiation changes in the adjacent tissues. Necrosis was found in 6 cases but was prominent in only 2, one of which was the only example of a mixed-cell tumour, the other 22 being spindle-cell tumours. Enucleation became necessary on average at about 32 months after treatment (23 out of 100 treated eyes) because of obvious failure of treatment with evidence of continued growth, or because of radiational complications leading to a painful blind eye. The 5-year survival rate was 86% compared with about 50% when the treatment is enucleation.

From 1960 to 1975 in the Oncology Clinic at Moorfields Eye Hospital 420 patients were seen with malignant melanoma of the choroid of which 300 were treated by primary enucleation and 100 by the application of a cobalt plaque. Others were treated by light coagulation, and in some cases, particularly in older people, no active treatment was given but the patient was kept under careful observation.

The purpose of this paper is to report 23 cases in which the eyes have been removed after cobalt plaque therapy for malignant melanoma of the choroid and to describe the histopathological changes.

Case reports

The ages of the patients varied between 30 and 75 years (average 51 years), and there were 14 males and 9 females. The interval between treatment by cobalt plaque therapy and enucleation of the affected eye varied from 7 months to 13 years and 10 months, but when the latter case is excluded the average interval was 32 months. The reasons for enucleation fell into 2 groups—failure of treatment with strong suspicion or clear clinical evidence of continued growth of the tumour, and radiation complications in the treated eye.

CASE 1

Female aged 47, presented in January 1962 with a malignant melanoma of the choroid affecting the infero-temporal quadrant of the left eye near the optic disc. A 10 mm cobalt plaque was applied, but the eye became blind and was enucleated 15 months after treatment. The patient is alive without recurrence 14 years after cobalt therapy.

Microscopical examination of the eye showed a spindle cell malignant melanoma of the choroid, with a moderate pigment content and a light reticulin content. There was no evidence of extraocular extension. A small area of necrosis was seen in the base of the neoplasm.

There was proliferation of the choroidal pigment adjacent to the growth, atrophy of Bruch's membrane and of the pigment epithelium over the tumour, subretinal exudate, and exudates in the detached retina overlying the melanoma.

CASE 2

This 59-year-old man had a large tumour at the posterior pole of his right eye treated by a 10 mm cobalt plaque. The eye was enucleated 10 months after treatment because of increasing size of the tumour. The patient is alive without recurrence 11 years after cobalt therapy.

Microscopical examination of the eye showed a spindle cell malignant melanoma of the choroid, having a moderate pigment and reticulin content.

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There was no evidence of necrosis, and extraocular extension was not seen.

There was thickening and narrowing of the posterior ciliary arteries, but the other structures were histologically normal in appearance.

CASE 3

Female aged 55, presented in 1963 with a history of blurred vision in the left eye for 3 months. A choroidal neoplasm was found in this eye, with a visual acuity of 6/12. A 15 mm cobalt plaque was applied, but postoperatively the mass increased in size and a retinal detachment developed. The eye was removed 2½ years after treatment and the patient died 5 years later, having survived 6 years after cobalt therapy. There was no recurrence of the tumour but the cause of death is unknown.

Microscopical examination of the eye showed a spindle cell malignant melanoma of the choroid with a moderate pigment and reticulin content. There was no evidence of necrosis, and extraocular extension was not seen. The tumour was infiltrated by a moderate number of lymphocytes.

There was detachment of the retina, with albuminous exudate in the subretinal space.

CASE 4

Female aged 66. In 1961 an infero-temporal mass was discovered in the left eye, which was kept under observation until 1965, when the vision suddenly decreased owing to secondary retinal detachment. By this time the mass was considered too large for conservative therapy, but enucleation was refused by the patient, and she was treated by light coagulation and the application of a 15 mm cobalt plaque. Four months after treatment vision was almost completely lost owing to a dense vitreous haemorrhage which slowly cleared, but in July 1966, 9 months after treatment, clinical examination showed active tumour and the eye was removed. She is alive without recurrence 11 years after cobalt therapy.

Microscopical examination of the eye showed a spindle cell malignant melanoma of the choroid, having a moderate pigment content and a light reticulin content. Small areas of necrosis were seen peripherally and at the apex. There was no evidence of extraocular extension.

There was pigment proliferation and atrophy of the adjacent choroid. Bruch's membrane and the pigment epithelium overlying the tumour showed atrophic changes, and the overlying retina showed an area of necrosis with pigment migration.

CASE 5

This 54-year-old man had a malignant melanoma of the choroid treated by cobalt plaque therapy in 1962. Five years later there was a large active tumour at the posterior pole and the eye was removed. He is alive without recurrence 14 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid, with a moderate reticulin content. Haemorrhages were present within the tumour, but there was no evidence of necrosis nor extraocular extension.

There was atrophy of Bruch's membrane and of the pigment epithelium overlying the tumour, and with detachment and atrophy of the retina in that region; haemorrhagic exudate was present in the subretinal space.

CASE 6

Female aged 38, presented with a choroidal malignant melanoma anterior to the equator in the upper temporal quadrant and under the lateral rectus. Two cobalt plaques (15 and 10 mm in diameter) were applied and light coagulation was also used. Three years after treatment the eye was removed because of severe necrosis of the sclera with threatened perforation of the globe. The patient is alive without recurrence 8 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid with a light reticulin content. There was no evidence of necrosis, and extraocular extension was not seen.

There was atrophy of the choroid and sclera adjacent to the tumour, and exudates and atrophic changes were seen in the retina overlying the neoplasm. There was atrophy of Bruch's membrane and of the overlying pigment epithelium.

CASE 7

Male aged 50. A choroidal malignant melanoma was discovered in the infero-nasal quadrant between the equator and optic disc of the left eye. Treatment was by a 10 mm cobalt plaque. Postoperatively the mass remained unchanged in size; the eye became blind with intraocular haemorrhage and secondary glaucoma, and was removed 14 months after treatment. The patient died from bronchopneumonia 4 years after cobalt therapy. There was no evidence of recurrence of the tumour.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma with a light reticulin content. A small area of necrosis was seen at the apex of the tumour, which also showed haemorrhages. There was no evidence of extraocular extension.

There was atrophy of Bruch's membrane and of the pigment epithelium overlying the tumour, and haemorrhage was present in the vitreous.

CASE 8

Male aged 55, presented with a malignant melanoma of the choroid in the infero-temporal quadrant of the right eye near the optic disc. He was treated with a 7·5 mm cobalt plaque; 14 months later the mass was clearly increasing in size, and the tumour was considered to be active. The eye was removed. The patient is alive without recurrence 7 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid, having a heavy reticulin content. There was no evidence of necrosis, and extraocular extension was not seen.

There were atrophic changes in the adjacent choroid, atrophic changes in the detached retina overlying the tumour, and exudate in the subretinal space.

CASE 9

Female aged 65, presented with a large choroidal tumour in the infero-nasal quadrant of her left eye near the optic disc. A 15 mm cobalt plaque was applied, and 15 months later a clinically active melanoma was evident, with increasing serous retinal detachment. The eye was removed 18 months after treatment. She is alive without recurrence 7 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid with a light reticulin content. There was no evidence of necrosis, and extraocular extension was not seen.

There was marked atrophy of the adjacent choroid, atrophy of the overlying Bruch's membrane and of the pigment epithelium, and exudates and atrophic changes in the overlying retina.

CASE 10

Male aged 54, presented in August 1967 with a large malignant melanoma of the choroid in the infero-temporal quadrant of his left eye, extending towards the macula. The right eye was normal. The tumour was considered to be too large for conservative therapy, but the patient refused enucleation and was therefore treated with a 15 mm cobalt plaque. He retained some vision in this eye until August 1969, when a massive choroidal and subretinal haemorrhage occurred, leading to secondary glaucoma and complete loss of vision. The eye was removed 2 years after treatment, at which time he also had massive liver metastases. He died 4 years after cobalt therapy.

Microscopical examination of the eye showed a mixed-cell malignant melanoma of the choroid, having a moderate content of pigment and reticulin. There was extensive haemorrhagic necrosis of the tumour, which showed infiltration by lymphocytes.

There was atrophy, haemorrhages, and pigment proliferation of the adjacent choroid, atrophy of the overlying Bruch's membrane and of the retinal pigment epithelium, and diffuse atrophy of the adjacent detached retina. The subretinal space contained haemorrhagic exudate.

CASE 11

Male aged 60. This patient was first seen in April 1967 with a large malignant melanoma of the choroid in the infero-nasal quadrant of his left eye extending up to the optic disc. Vision in this eye was 6/6 but in the right eye vision was reduced to 6/60 as a result of concussional damage to the retina following an injury by a tennis ball at the age of 24. The left eye was his only useful eye, therefore, and was treated by means of a 10 mm cobalt plaque with an overlapping C-shaped plaque. In April 1968 the vision was 6/18 and the mass was smaller but still active. In January 1969, 20 months after treatment, he presented with complete loss of vision in the treated eye owing to ischaemia of the optic nerve and retinal artery. The eye was removed in December 1969, 29 months after treatment. The patient died in March 1970 from endocarditis and septicaemia, 3 years after cobalt therapy. There was no evidence of tumour recurrence.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid, with a light reticulin content. There was no evidence of necrosis, and extraocular extension was not seen.

The adjacent choroid showed sclerotic narrowing of its vessels, with atrophy and pigment proliferation. Atrophic changes were seen in the overlying Bruch's membrane and the pigment epithelium, and exudates and atrophic changes were seen in the overlying retina. The vitreous contained haemorrhages. There was thickening and narrowing of the posterior ciliary arteries.

CASE 12

Male aged 56. This patient was first seen by his optician in 1965, who found a pigmented lesion in the left fundus which was thought to be an area of inactive choroiditis. In October 1969 he complained of blurred vision in his left eye of 3 weeks' duration. Vision was 6/9 and in the lower temporal quadrant there was a protuberant collar-stud choroidal melanoma with a small associated secondary retinal detachment. The right eye was normal. It was thought that the height of the lesion in his left eye precluded conservative therapy, but as the vision was still good a 10 mm cobalt plaque was applied. Subsequently the mass appeared to regress slightly, but the secondary retinal detachment extended, vision deteriorated, and the eye was removed 18 months after treatment, by which time it was completely blind and divergent with a total retinal detachment, rubeosis, and cataract. He is alive without recurrence 7 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, predominantly spindle cell malignant melanoma of the choroid, with a heavy reticulin content. There were small areas of necrosis at the base on either side and near the apex. There was no evidence of extraocular extension.

The adjacent choroid showed sclerosed vessels, pigment proliferation, and atrophy. There were atrophic changes of Bruch's membrane and the pigment epithelium overlying the tumour, and the detached retina showed exudates and haemorrhages. The subretinal space contained albuminous exudate.

CASE 13

Male aged 53, presented in October 1966 with a history of flashing lights in his left eye for 6 months and loss of the lower field of vision 4 weeks previously. The right eye was normal with vision 6/6. Vision in the left eye was reduced to counting fingers and there was a massive tumour in the temporal half of the fundus with extensive serous retinal detachment. He refused enucleation and was treated with a 10 mm cobalt plaque in November 1966. Four months later the detachment had disappeared and it was thought that the tumour was smaller. At this time he showed epilation of the eyebrow hair on the side where the plaque had been placed and by August 1967, 9 months after treatment, he had an established radiation keratopathy with a typical dry-eye syndrome due to decreased tear secretion. Vision was down to 6/60 and further regression of the tumour was noted. In February 1971 vision was reduced to counting fingers with extensive intraocular haemorrhage, and by December 1971 the eye was blind and painful with intraocular haemorrhage, gross rubeosis, dense cataract, and increased intraocular pressure. In March 1972, because of severe pain, the eye was removed. He is alive without recurrence 10 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid with a light reticulin content. Haemorrhages were seen in the tumour, but there was no evidence of necrosis or of extraocular extension.

There were haemorrhages and pigment proliferation in the adjacent choroid, atrophy of the overlying Bruch's membrane and pigment epithelium, and detachment of the overlying retina, which showed thickened, narrowed vessels, exudates, haemorrhages, atrophic changes, and pigment migration. Subretinal haemorrhagic exudate was present.

CASE 14

Male aged 50, presented in July 1970 with a 3-month history of a gradual onset of distorted vision, micropsia, and more recent blurring of vision. The left eye was normal. Right vision was down to 6/36 and a large melanoma was found adjacent to the posterior pole in this eye. A 10 mm cobalt plaque was applied, and in June 1971 vision was down to 6/60 and there was a marked radiation keratopathy, but the mass appeared to have regressed to some extent. In September 1971, however, a serous retinal detachment appeared, and the tumour was considered to be still active. The eye was removed in April 1972, 20 months after treatment. The patient is alive without recurrence 6 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid, with a heavy reticulin content. There was no evidence of necrosis, and extraocular extension was not present.

There was atrophy and pigment proliferation of the adjacent choroid, atrophy of the overlying Bruch's membrane and the pigment epithelium, and detachment of the retina, which showed exudates, atrophy, and some pigment migration.

CASE 15

Male aged 44. This man was first seen in November 1968 with a 3-month history of blurred vision in the upper temporal field of his left eye. Examination showed a visual acuity of 6/6 in each eye, and in the left eye a bulky choroidal neoplasm with a small secondary detachment was found on the nasal side of the fundus near the optic disc. It was considered too large and too near the optic disc for cobalt plaque therapy. The patient refused enucleation and insisted on conservative treatment, having been warned that he would certainly lose vision owing to the proximity of the neoplasm to the optic nerve. A 15 mm cobalt plaque was applied in December 1968 and 3 months later the detachment had cleared completely and the mass was smaller with vision retained at 6/9. By November 1970 vision had deteriorated slightly to 6/12 but had dropped to 6/60 by May 1971. In September 1971 the eye was blind with chronic uveitis, posterior synechiae, and extensive choroido-retinal degeneration. Fluorescein angiography in December 1971 showed that there was still active tumour, and in April 1972, 3½ years after treatment, the eye, which by then was painful as well as blind, was removed. He is alive without recurrence 7 years after cobalt therapy.

Microscopical examination of the eye showed a heavily pigmented, spindle cell malignant melanoma of the choroid with a heavy reticulin content. There was extensive necrosis, but no evidence of extraocular extension was seen.

There was atrophy and pigment proliferation of the adjacent choroid, atrophy of the overlying Bruch's membrane and the pigment epithelium, and sclerosed vessels, exudates, necrosis, and atrophy of the overlying retina.

CASE 16

Male aged 49, presented in March 1971 with a 4-week history of visual distortion followed by a shadow over the left visual field. Visual acuity was 6/5 in each eye. In the left eye a choroidal melanoma was found in the lower temporal quadrant and a 7·5 mm cobalt plaque was applied. Five months later vision was down to 6/18, the retinal detachment had disappeared, and the mass was smaller; in March 1972 the detachment recurred and fluorescein angiography suggested that the tumour was still active. The eye was removed 2 months later, 1 year after treatment. The patient is alive without recurrence 5 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid with a light reticulin content. There was no evidence of necrosis, and extraocular extension was not seen.

There was atrophy of the overlying Bruch's membrane and pigment epithelium, haemorrhages and atrophic changes of the detached retina, and haemorrhagic exudate was present in the subretinal space.

CASE 17

Female aged 40. This patient was first seen in October 1970 with a 2-week history of shimmering vision in the right eye, preceded by floating spots for several months. Right vision was down to 6/24 and there was a solid mass in the postero-equatorial fundus on the temporal side, with a shallow detachment extending towards the macula. A 10 mm cobalt plaque was applied and 5 months later the mass was showing signs of regression with complete resolution of the detachment. The lesion appeared to have increased in size in August 1972, and fluorescein angiography indicated an active tumour; the right eye was removed in November 1972. She is alive without recurrence 6 years after cobalt therapy.

Microscopical examination of the eye showed a heavily pigmented, spindle cell malignant melanoma of the choroid, with a moderate reticulin content. There was no evidence of necrosis and extraocular extension was not seen.

There was atrophy and pigment proliferation of the adjacent choroid, atrophy of the overlying Bruch's membrane and the pigment epithelium, and detachment of the retina, which showed exudates, atrophy and some pigment migration.

CASE 18

Female aged 37, presented in August 1970 with a 3-month history of distorted vision in the right eye due to a malignant melanoma of the choroid on the temporal side, with a secondary serous detachment reducing vision to 6/9. A 10 mm cobalt plaque was applied, with improved visual acuity as the detachment disappeared. 18 months later vision had dropped to 6/60 with enlargement of the choroidal mass and recurrence of the detachment. From the clinical signs and fluorescein angiography the tumour was regarded as being still active, and the eye was removed 3 years after treatment. She is alive without recurrence 6 years after cobalt therapy.

Microscopical examination of the eye showed a spindle cell malignant melanoma of the choroid with a marked pigment content and heavy reticulin content. There was no evidence of necrosis, and extraocular extension was not seen. A small number of lymphocytes infiltrated the tumour.

There was atrophy and pigment proliferation of the adjacent choroid and atrophy of the overlying Bruch's membrane and the pigment epithelium. The overlying retina was detached and showed exudates and atrophic changes. The subretinal space contained albuminous exudate.

CASE 19

Male aged 45. A greyish swelling was found in the lower temporal quadrant of the left eye at a routine sight test which showed normal vision. In August 1963 a 10 mm cobalt plaque was applied, and the tumour regressed. Three years later vision was 6/18 and the lesion appeared inert. In January 1970 vision dropped suddenly owing to a vitreous haemorrhage, and when this cleared numerous retinal haemorrhages and vascular changes were seen near the irradiated area. In February 1972 vision was down to 6/60; the lesion appeared elevated again and fluorescein angiography suggested that the tumour was active. 12 months later vision had dropped to hand movements only, and shortly afterwards glaucoma developed owing to irreversible vascular complications; the eye was removed. He is alive without recurrence 13 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid with a light reticulin content. There was no evidence of necrosis, and extraocular extension was not seen. Haemorrhage was present within the tumour.

There was atrophy and pigment proliferation of the adjacent choroid, atrophy of the overlying Bruch's membrane and pigment epithelium, and diffuse necrosis of the overlying detached and haemorrhagic retina. Haemorrhage was seen in the subretinal space and vitreous.

CASE 20

Male aged 36, presented in May 1969 with floating spots in the right eye for 3 months and a choroidal swelling which was discovered by his optician. The vision was 6/6 and a malignant melanoma with a small serous detachment was present on the nasal side of the fundus. This was treated by a 15 mm cobalt plaque. 12 months later the vision was 6/6 and the tumour appeared inert. Two years later the vision had decreased to 6/18 over a few months and numerous retinal haemorrhages were present. In September 1972 there was a large haemorrhage at the macula, and in December 1973 a massive vitrous haemorrhage occurred, reducing vision to light perception only. Two months later the eye was virtually blind, with dense vitreous haemorrhage preventing any view of the fundus. The eye was removed. The patient is alive without recurrence 7 years after cobalt therapy.

Microscopical examination of the eye showed a spindle cell malignant melanoma of the choroid, having a moderate pigment and reticulin content. There was no evidence of necrosis, and extraocular extension was not seen.

There was a normal choroid, and some atrophy of the overlying Bruch's membrane, pigment epithelium, and retina. Some haemorrhage was present in the vitrous.

CASE 21

Male aged 30. This patient noticed blurred vision in his left eye for 3 months, which was due to a malignant melanoma on the temporal side with an extensive inferior retinal detachment. A 10 mm cobalt plaque was applied in April 1969, and the detachment rapidly regressed. In June 1971 the vision was 6/9 and the mass appeared inert, although still slightly elevated. 12 months later the vision had dropped to 6/18 with a recurrence of the serous retinal detachment, and fluorescein angiography suggested that the tumour was active. In February 1974 the detachment had extended, with reduction of vision to 6/60, and the eye was removed 4½ years after treatment. He is alive without recurrence 7 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid with a moderate reticulin content. There was no evidence of necrosis or of extraocular extension.

There was pigment proliferation of the adjacent choroid and atrophy of the overlying Bruch's membrane and pigment epithelium. The overlying detached retina showed atrophy and small haemorrhages, and the subretinal space contained haemorrhagic exudate.

CASE 22

This 75-year-old woman had a malignant melanoma of the choroid in her left eye, which was kept under observation for 2 years before the application of a cobalt plaque; this was followed by some episcleral necrosis and failure of the tumour to respond. The eye was enucleated 7 months after the application of the plaque, and she is alive without recurrence 1 year after cobalt therapy.

Microscopical examination of the eye showed a spindle cell malignant melanoma of the ciliary body and choroid with a moderate content of pigment and reticulin. There was no evidence of necrosis or of extraocular extension.

There was some superficial episcleral necrosis overlying the tumour. The adjacent choroid showed atrophic changes and pigment proliferation, and atrophic changes were also present in the overlying Bruch's membrane, pigment epithelium, and retina.

CASE 23

Female aged 50. A malignant melanoma of the choroid was treated with a cobalt plaque in 1961 and light coagulation in 1962, after which the vision was reduced to hand movements. A prominent swelling remained but without clinical signs of activity until March 1975, when a large vitreous haemorrhage occurred with loss of light perception; the eye was removed. She is alive without recurrence 15 years after cobalt therapy.

Microscopical examination of the eye showed a lightly pigmented, spindle cell malignant melanoma of the choroid with a heavy reticulin content. There was no evidence of extraocular extension or of necrosis, but extensive haemorrhage was seen within the tumour.

There was extensive atrophy of the adjacent choroid and extensive atrophy of the overlying Bruch's membrane, pigment epithelium, and detached retina. Extensive haemorrhage was present in the vitreous and subretinal space.

A summary of the pathological findings is shown in Tables 1 and 2 and of the survival rate in Table 3.

Table 1 *Summary of pathological findings in 23 cases of malignant melanoma of choroid*

Cell type		
(a) Spindle	22	(Cases 1–9, 11–23)
(b) Epithelioid	0	
(c) Mixed	1	(Case 10)
Pigment content		
(a) Light	13	(Cases 5–9, 11–14, 16, 19, 21, 23)
(b) Moderate	7	(Cases 1–4, 10, 20, 22)
(c) Heavy	3	(Cases 15, 17, 18)
Reticulin content		
(a) Light	9	(Cases 1, 4, 6, 7, 9, 11, 13, 16, 19)
(b) Moderate	8	(Cases 2, 3, 5, 10, 17, 20–22)
(c) Heavy	6	(Cases 8, 12, 14, 15, 18, 23)
Necrosis		
(a) More than 50% of tumour	2	(Cases 10, 15)
(b) Less than 50% of tumour	4	(Cases 1, 4, 7, 12)
(c) None	17	(Cases 2, 3, 5, 6, 8, 9, 11, 13, 14, 16, 17, 18 19, 20, 21, 22, 23)
Haemorrhages	6	(Cases 5, 7, 10, 13, 19, 23)
Lymphocytic infiltration	3	(Cases 3, 10, 18)

Table 2 *Summary of pathological findings: remaining ocular structures*

Posterior ciliary arteries (thickened and narrowed)	2	(Cases 2, 11)
CHOROID (adjacent to tumour)		
(a) Sclerosed vessels	2	(Cases 11, 12)
(b) Pigment proliferation	13	(Cases 1, 4, 10–15, 17–19, 21, 22)
(c) Atrophy	14	(Cases 4, 6, 8–12, 14, 15, 17–19, 22, 23)
(d) Haemorrhages	2	(Cases 10, 13)
Atrophy of Bruch's membrane (overlying tumour)	20	(Cases 1, 4–7, 9–23)
Atrophy of pigment epithelium (overlying tumour)		
RETINA (overlying tumour)		
(a) Detached	14	(Cases 1, 3, 5, 8, 10, 12–14, 16–19, 21, 23)
(b) Sclerosed vessels	2	(Cases 13, 15)
(c) Exudates	9	(Cases 1, 6, 9, 11–13, 15, 17, 18)
(d) Haemorrhages	5	(Cases 12, 13, 16, 19, 21)
(e) Necrosis	3	(Cases 4, 15, 19)
(f) Atrophy	16	(Cases 5, 6, 8–11, 13–18, 20–23)
(g) Pigment migration	4	(Cases 4, 13, 14, 17)
Haemorrhage in subretinal space	7	(Cases 5, 10, 13, 16, 19, 21, 23)
Vitreous haemorrhage	5	(Cases 7, 11, 19, 20, 23)

Table 3 *Survival rate*

Number of patients	*Dead*		*Five-year survival rate*
	From tumour	*Other causes*	
23	1	3	86%

Discussion

For many years the usual treatment of cases of choroidal malignant melanoma has been enucleation of the affected eye. Generally the decision for enucleation presents no difficulty and is accepted by the patient. In some cases, however, because of its position and size when discovered, the tumour may not seriously impair vision or may be found in what is, for practical purposes, the patient's only eye; in these circumstances the patient may refuse enucleation. Furthermore, the advantage of enucleation in terms of increased life expectancy is not firmly established. Many attempts have been made, therefore, to develop methods of conservative treatment for this type of malignant disease, whereby the tumour may be destroyed and some useful vision preserved in the treated eye.

The methods adopted have included destruction of the neoplasm by *diathermy* (Weve, 1935; Goldsmith, 1943; Melchers, 1953; Boniuk and Girard, 1965; Davidorf *et al.*, 1970); *ionising radiation* using radon seeds (Moore *et al.*, 1931; Newman *et al.*, 1970), radium discs (Stallard, 1952), cobalt-60 gamma-ray applicators (Stallard, 1959, 1968; Bedford, 1968; Long *et al.*, 1971), and ruthenium-106 beta-ray applicators (Lommatzsch, 1973); *light coagulation* (Meyer-Schwickerath, 1961; Lund, 1962, 1966; Curtin and Norton, 1963; Makley *et al.*, 1965; Hepler *et al.*, 1968; Francois, 1965, 1968a and b; Dufour *et al.*, 1968; Vogel, 1972, 1973), and *cryotherapy* (Lincoff *et al.*, 1967; Campinchi, 1968; Davidorf *et al.*, 1970). Others have attempted to save the eye by *surgical techniques* as by choroidectomy (Stallard, 1973). In recent years there has developed a policy of no active intervention but careful observation of patients with initially small asymptomatic melanomata and good vision, particularly in the elderly, provided there is no evidence of extension or involvement of other intraocular structures (Curtin and Cavender, 1974; Zimmerman and McLean, 1975).

That cobalt plaque therapy is highly effective in cases of retinoblastoma is not in doubt (Bedford *et al.*, 1971), but in cases of malignant melanoma of the choroid the success rate is less and the complication rate high, particularly loss of vision due to retinal vascular occlusion and optic nerve ischaemia (MacFaul and Bedford, 1970; Bedford *et al.*, 1970). Furthermore, it is now clear that some tumours do not respond at all to cobalt plaque therapy. After a period of apparent regression the neoplasm shows signs of continued growth with recurrence of serous retinal detachment, with increase in size, or with intraocular haemorrhage; the eye must then be removed. On the other hand enucleation may become necessary because of radiational complications leading to a painful blind eye even though the neoplasm appears clinically to have been destroyed. In cases which do respond with regression to a more or less flat scar there are after many months distinctive and progressive vascular changes in the fundus around the base of the tumour, which may take up to 2 years or more to mature, and it is now thought that in those successful cases regression is caused by progressive radiation-induced ischaemia rather than by the direct cytotoxic effect of radiation on the tumour (Bedford, 1973).

Enucleation became necessary in 23 of our 100 cases treated by cobalt plaque therapy at Moorfields Eye Hospital, and histological examination of these eyes has shown that in 17 eyes there was no evidence of necrosis in the tumour, although there was clear evidence of radiation-induced changes in the adjacent tissues. In 6 eyes, signs of necrosis were found, but the extent of necrosis could not be correlated with cell type, pigment content, or reticulin content. However, the one example of a mixed cell melanoma did show extensive necrosis, whereas 17 out of the 22 spindle cell tumours showed no necrosis. Of the 2 cases showing extensive necrosis lymphocytic infiltration was found in 1 case (case 10), suggesting an immunological response; in the other 2 cases with similar infiltration necrosis was not evident.

The expression of the overall prognosis in percentages following enucleation for malignant melanoma is difficult. In general, however, the 5-year survival rate is about 50% (Duke-Elder and Perkins, 1966). In our series the 5-year survival rate following cobalt therapy was 86%.

In a future report of the results of treatment for malignant melanoma of the choroid it is proposed to consider the possible reasons for failure of treatment in these cases in detail, but it is relevant here to note that several of the cases were deemed unsuitable for conservative treatment in view of the size and position of the tumour, but cobalt plaque therapy was applied in most of them because the patient refused to accept enucleation.

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Medulloepithelioma (diktyoma) presenting as a perforated, infected eye

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SUMMARY A case of embryonal medulloepithelioma (diktyoma) presenting with perforated infected eye in a 13-year-old Black African girl is described. The tumour mass occupied most of the deformed eye, and invasion of the sclera anteriorly was seen. There was no evidence of orbital or distant tumour involvement. It is suggested that with increasing age these tumours are more likely to show frankly malignant features.

Medulloepithelioma (diktyoma) is a rare neoplasm of the eye which is characterised by slow growth and local invasion and is composed of glandular, neural, and mesenchymal elements (Andersen, 1962). It presents even rarely as an infected perforated eye with a fungating mass replacing the ocular contents. Soudakoff (1936) reported the case of a 28-year-old Chinese who had a perforated eye with tumour mass completely filling it. This paper reports the case of a young black African girl who presented with perforation of one eye and orbital cellulitis initiated probably by a recent rapid growth of a medulloepithelioma (diktyoma) which filled the eye and invaded the cornea.

Case report

A 14-year-old adolescent girl of the Makonde tribe was seen as a referred case in July 1971 for evaluation and treatment of a probable neoplastic growth in the left eye. There had been complete loss of vision in that eye for three months. The eye had become progressively enlarged, protuberant, and painful and had ruptured spontaneously. Pus discharge had been noticed for a week. The patient was reported to have had poor vision in the left eye since 3 years of age; a white spot had been visible through the pupil; the left eye had been the same size as the right. Until 3 months before admission to hospital there had been no apparent progression of the disease. The family history contained nothing relevant to this case.

Examination showed cellulitis of the left orbit, an anteriorly perforated left eye, with loss of cornea, purulent discharge, and a fragmenting mass of irregular brownish-grey tissue attached mainly to the superior and temporal portion of the eye and extending into the posterior chamber. The infection was controlled with systemic antibiotics and the left eye was enucleated. Radiological examination of the skull showed no orbital involvement, and chest *x*-rays were normal. Postoperative recovery was uneventful. There was no evidence of tumour recurrence at 6 months, and the patient was subsequently lost to follow-up.

Pathological findings

The left eye measured 33×27×26 mm. There was a large anterior perforation with loss of cornea, part of conjunctiva, and sclera. Pus and exudate were present on the ragged perforation edges. Bulbar conjunctiva and parts of the sclera were also covered with fibrinous exudate. The eye was deformed and on sectioning showed extensive disorganisation of the contents. A solid fragmenting tumour mass filled the anterior half of the eye (Fig. 1). The tumour was brown to grey, the anterior portion was covered with pus, and some areas felt mucoid. Detached retina occupied part of the posterior portion. On gross examination there was no penetration of the sclera away from the perforation margins.

Microscopically the tumour consisted mainly of an array of glandular structures varying widely in size, shape, and configuration. The gland spaces contained lightly haematoxyphilic hyaline material resembling vitreous (Fig. 2). The glands and interlacing cords were lined with crowded columnar

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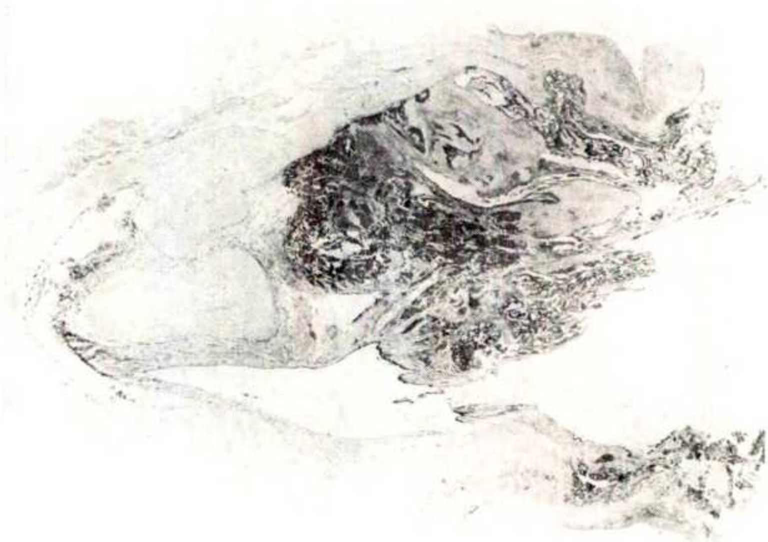

Fig. 1 *Section of the whole eye showing the tumour mass, disorganised orbital contents, and the anterior perforation (haematoxylin and eosin, ×3)*

cells with basally placed ovoid hyperchromatic nuclei. Many mitoses were seen, but no abnormal ones were identified. The cells were supported on well defined limiting membrane, and there was little intervening stroma. Cellular debris was seen in the hyaline membrane.

Irregularly interspersed with the glandular tissue were areas containing solid sheets of cells, and in some places the glands seemed to merge with the solid zones. The solid areas consisted partly of polygonal cells with cytological resemblance to the cells forming the glands. There were irregular cleft-like spaces without any hyaline material. At their junction with glandular tissue these cells formed columns merging with the glands. Mitoses were frequent but variable. Clumps of melanin pigment

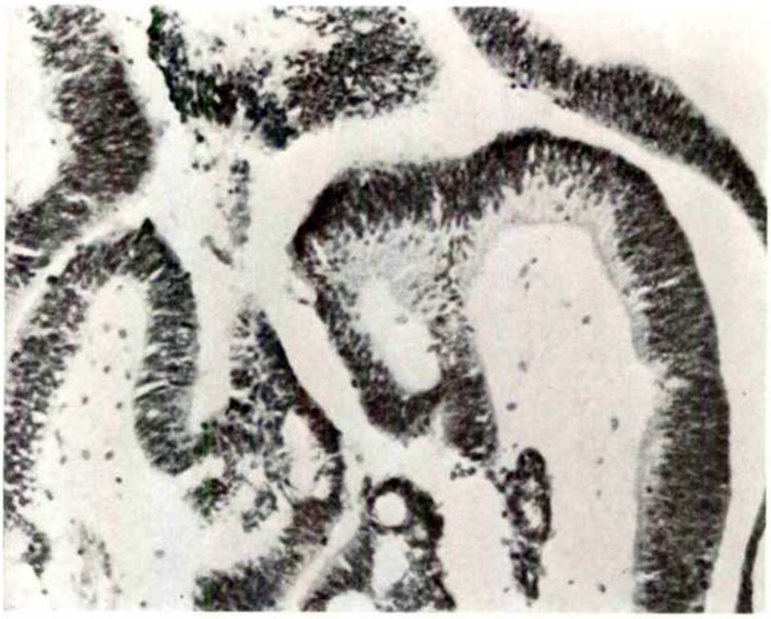

Fig. 2 *Glandular spaces of varying size, lined by crowded columnar epithelial cells with limiting membranes. Hyaline material with cell debris fills the spaces (haematoxylin and eosin, ×125)*

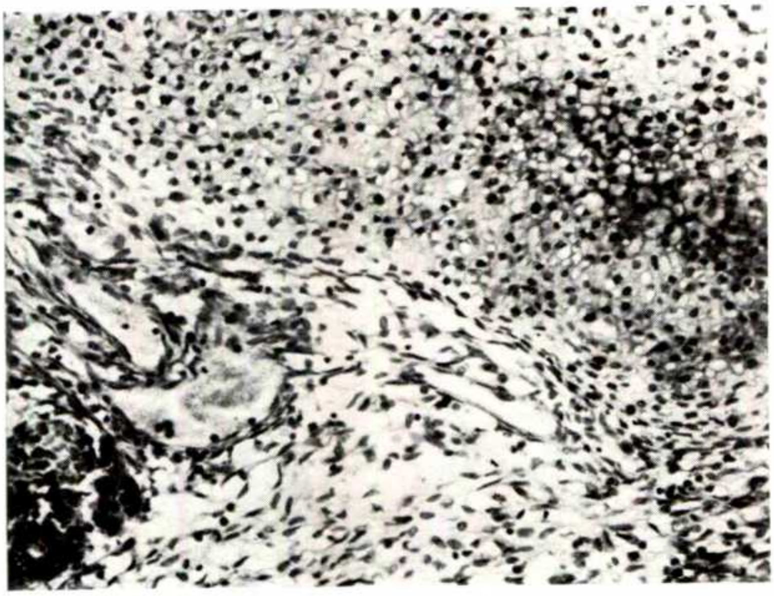

Fig. 3 *The spindle cells are seen to merge with the cartilage cells. Sinusoidal spaces surrounded by spindle cells are present in the lower half (haematoxylin and eosin, ×350)*

occurred intercellularly and also in groups of cells, whose cytologic features were obscured by the pigment (Fig. 3). Forming part of the solid areas were spindle cells with ovoid nuclei containing vesicular chromatin. A few sinusoidal spaces were present in these areas and were lined by the spindle cells. Mitoses were rare. In two places there were islands of haematoxyphilic hyaline cartilage. The spindle cells merged with the chondroid elements at the periphery of the islands (Fig. 3). The chondroid cells were uniform in appearance and no mitoses were observed. In several areas there were groups of spongioblasts, which had indistinct cytoplasmic boundaries and rounded, relatively large nuclei with a moderate mitotic activity (Fig. 4). Calcific foci, rhabdomyoblasts, or ganglion cells were not detected. Tissue sections from the perforation margins showed corneal keratinisation and thickening, chronic granulation tissue, and necrotic debris. Glandular tumour tissue could be identified in the partially necrotic areas, and small foci of neoplastic glands were seen in the conjunctival and scleral tissues.

Discussion

The history in this case indicates that the tumour or an abnormal mass was in the eye from 3 years of age without any noticeable progression until recently. It is, however, not known whether the patient had a progressive loss of vision in the left eye over the years. Histological features are suggestive of active, proliferative neoplastic tissue, and it is probable that the tumour had undergone recent rapid growth after a long initial, relatively quiescent period, with the glandular component exhibiting more aggressive invasive characteristics, leading to perforation of the eye. The nature of the stimulus or stimuli leading to this change is speculative. In the group of embryonal type of medulloepitheliomas reviewed by Andersen (1962) the mean duration of symptoms before diagnosis was 4 months with a range of up to 3 years for benign tumours and a mean duration of 1 year with a range of 2 months to 9 years for malignant tumours. In all these cases the tumours appeared histologically to be at least

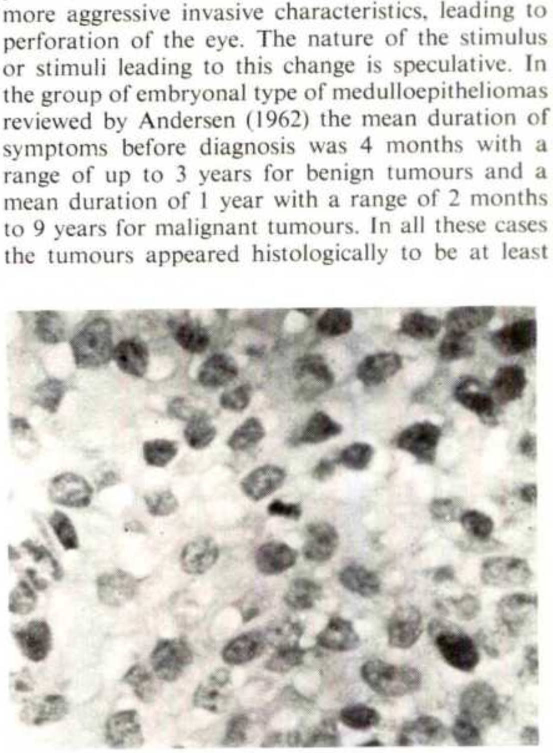

Fig. 4 *Spongioblasts with mitotic activity (haematoxylin and eosin, ×500)*

locally invasive, and the malignant ones were so characterised mainly because of extraocular, orbital invasion, pronounced pleomorphism, mitotic activity, and an absence of ganglion cells. The present case had all these features except orbital invasion. Cardell and Starbuck (1959), in reviewing cases of medulloepitheliomas (diktyomas), found that advanced tumours with retinal or scleral involvement presented in older age groups. It is likely therefore that with increasing age the tumour may show characteristics of frank malignancy and that, left alone one, or more of the cellular elements may exhibit features of vigorous growth and tissue invasion extraocularly.

Andersen (1962) has suggested that the chondroid and spindle-cell components are part of stromal reaction to the tumour, possibly in the persistent primary vitreous. Zimmerman *et al.* (1972) reported 4 cases of medulloepithelioma containing rhabdomyosarcomatous component, and in one of these the recurrent orbital tumour had chondrosarcoma tissue only. They suggested that the primitive medullary epithelium is pluripotential. In the present case the chondroid and spindle cell mesenchymal components did not exhibit pleomorphism or mitotic activity, and no rhabdomyoblasts or ganglioform cells were found. On electron microscopy the ganglioform cells were reported by Zimmerman *et al.* (1972) to have features of rhabdomyoblasts.

In reviewing a group of orbital tumours in African children in the geographical area in which the patient presented Templeton (1971) did not record any case of embryonal medulloepithelioma. This is believed to be the first such case from the area.

I thank Dr C. Anderson for confirming the diagnosis and discussion of the case.

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Experimental internuclear ophthalmoplegia

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SUMMARY A midline experimental lesion separating the medial longitudinal fasciculi at and below the level of the abducens nuclei without damaging either fasciculus at the level of the nuclei has produced defects of ocular motility resembling those of clinical internuclear ophthalmoplegia. Electromyographic recordings during lateral gaze demonstrate: (1) lack of inhibition of the lateral rectus muscle in the adducting eye, (2) delayed inhibition of the medial rectus muscle in the abducting eye, and (3) occasional evidence of excitation of the medial rectus muscle of the abducting eye probably associated with pupillary constriction. The presumed physiologic mechanisms involved in conjugate gaze movements are discussed in the light of the experimental findings.

Internuclear ophthalmoplegia (INO) is the dissociation of ocular movements during horizontal versions, consisting of an underacting medial rectus muscle (in the adducting eye), often accompanied by abducting nystagmus of the fellow eye. The presence of this movement disorder is considered to be pathognomonic of a lesion in the medial longitudinal fasciculus (MLF) in the brainstem. The pathophysiologic mechanism by which the dissociated nystagmus of the abducting eye is produced has remained elusive. Stroud *et al.* (1973, 1974) proposed that asymmetric convergence is used to drive the weak medial rectus muscle, which secondarily produces the abducting nystagmus on the uninvolved side. More recently, Pola and Robinson (1976) have postulated that a lesion of one MLF would interrupt both ipsilateral excitatory and contralateral inhibitory fibres to the respective medial rectus subnuclei of the third cranial nerve. This postulate would fit well with clinical findings previously reported by Loeffler *et al.* (1966). In contrast to Stroud *et al.* these authors believe that the nystagmus of the abducting eye after a contralateral MLF lesion is due to loss of inhibition of the medial rectus activity of that eye. A third hypothesis attributes the nystagmus to interruption of nerve fibre pathways passing to the abducens nucleus of the abducting eye (Carpenter and Strominger, 1965).

The purpose of this study was to produce an experimental model of inter-nuclear ophthalmoplegia in the primate without damaging the parapontine gaze centres or their subservient ocular motor nuclei. The animals were studied by electromyography in order to gain an understanding of the underlying pathophysiology of INO.

Methods

Four male and one female rhesus monkeys of weights ranging from 9·5 to 12·5 lb (4·3 to 5·7 kg) underwent suboccipital craniectomy under barbiturate anaesthesia. In each case the cerebellar vermis overlying the caudal portion of the fourth ventricle was split in the midline to a depth of approximately 1·5 cm. Under magnification the two cerebellar hemispheres were held apart in this region, and a midline cut was made in the floor of the fourth ventricle with a fine knife.

A week or more after surgery the animals were studied in a primate chair with and without head restraint. Motion pictures, 8 and 16 mm, were made of the extraocular movements of all animals. Time projection comparisons were made to estimate the speed of movement in all animals. In addition all animals were re-studied during electromyography, at which time simultaneous recordings were made from 2 to 4 of the horizontal rectus muscles.

The following ocular motor functions were studied

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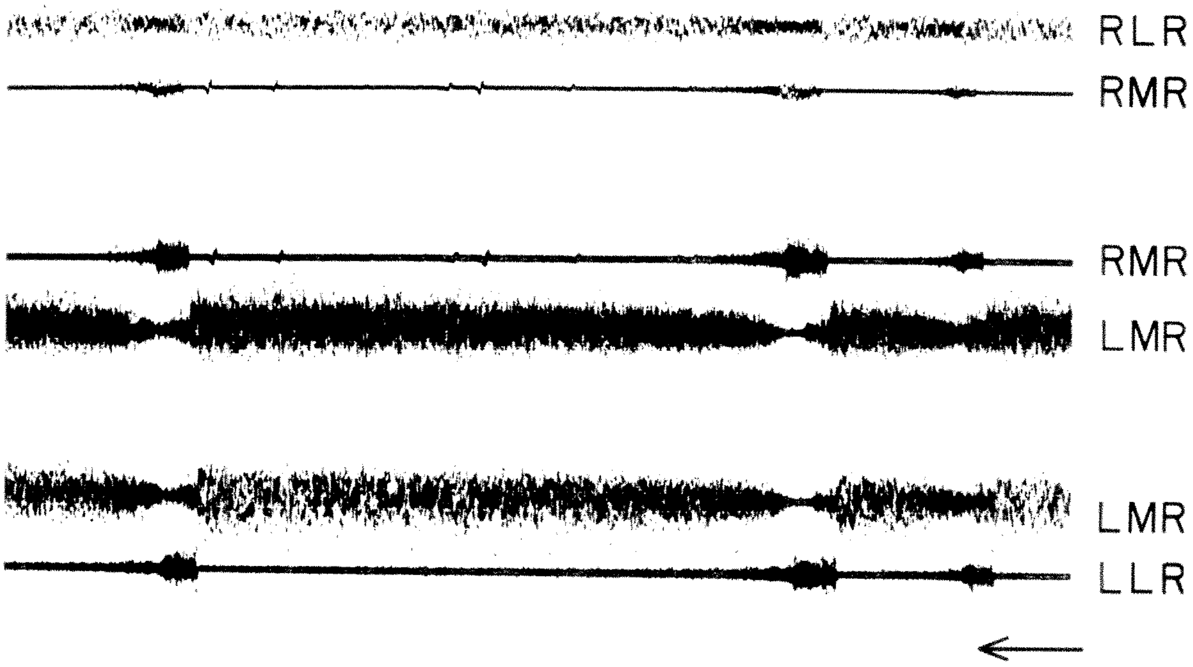

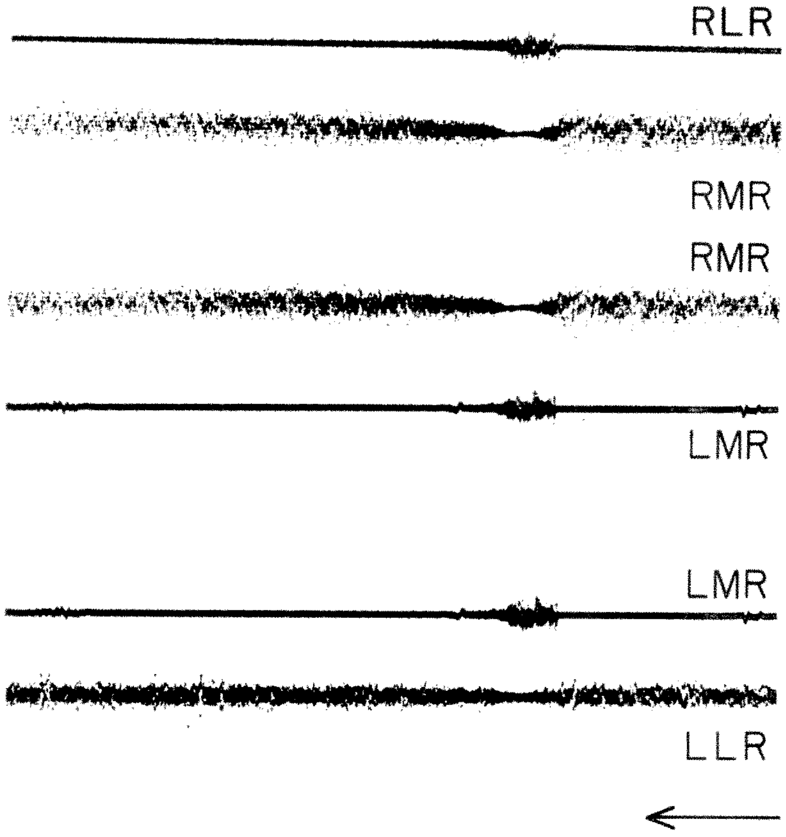

Figs. 1 and 2 *The EMG records are developed from the 6-channel recordings in pairs and then appropriately matched in order to assure accurate timing. Voltages have been adjusted in order to obtain similarity of records for qualitative comparison. These records reflect time moving from right to left.*

The following findings are demonstrated with saccadic movement to the left (Fig. 1): (1) *Failure of inhibition of the right lateral rectus muscle (RLR)*; (2) *delayed inhibition of the left medial rectus (LMR) muscle; and* (3) *a suggestion of delay to peak discharge in the right medial rectus muscle*

The following findings are demonstrated with saccadic movement to the right (Fig. 2): (1) *Failure of inhibition of the left lateral rectus muscle (LLR)*; (2) *delayed inhibition of the right medial rectus (RMR) muscle; and* (3) *a suggestion of delay to peak discharge in the left medial rectus muscle.*

(RLR—right lateral rectus; RMR—right medial rectus; LMR—left medial rectus; LLR—left lateral rectus.)

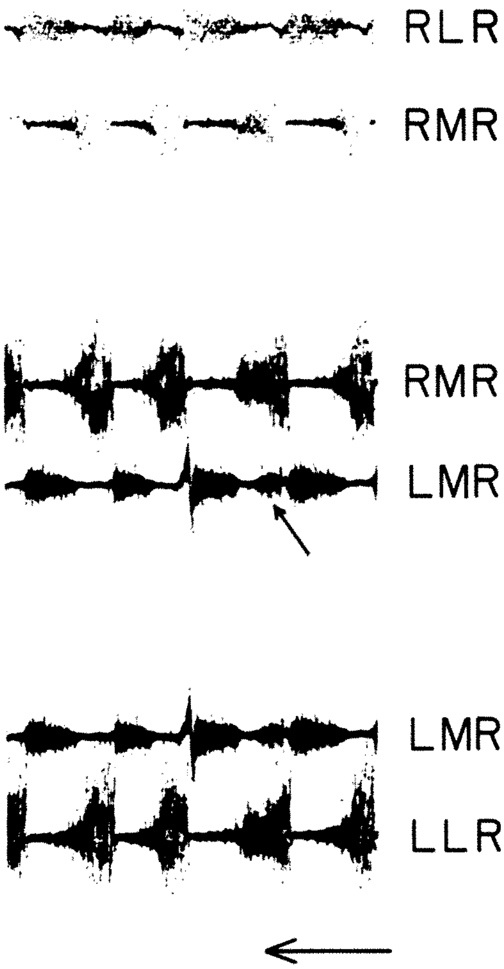

Fig. 3 *Co-firing of the left medial rectus muscle during saccadic (see arrow) movement to the left (RLR—right lateral rectus; RMR—right medial rectus; LMR—left medial rectus; LLR—left lateral rectus)*

in almost all of the cases: (1) Spontaneous gaze (i.e., the presence or absence of nystagmus, strabismus, skew deviation, conjugate gaze weakness or deviation); (2) horizontal and vertical saccades; (3) following movements; (4) convergence; (5) horizontal and vertical optokinetic nystagmus; (6) oculocephalic reflexes, and (7) cold water caloric testing (30°C).

A special canaliculus extension earpiece of Teflon tubing (1 mm internal diameter) was threaded into the external auditory canal of each animal to ensure adequate caloric stimulus delivery. 15 ml of water was then flushed into the external ear in approximately 15 seconds.

The animals were killed under deep barbiturate anaesthesia by intracardial perfusion with 3000 ml of 10% formalin in saline. The perfusion was accomplished by means of a Mayo roller pump adjusted to deliver 200–400 ml/minute. The brains were removed and stored in 10% formalin for a minimum period of three months and the brainstem imbedded in paraffin. Transverse 50 μm serial sections were made from the inferior olivary nuclei to the level of the third nerve nucleus. Every tenth section was stained with either Weigert's or Bodine's stain. Additional sections were stained and studied as deemed necessary.

Results

Clinically four of the five animals showed bilateral INO, which was relatively symmetrical but present only in far lateral gaze. Three of the four animals with INO had normal saccadic movements within the range they normally moved their eyes. Other neurological functions were normal except that one of these animals had ptosis and a slightly enlarged pupil on the left side. All vertical eye movements, both saccadic and following, as well as convergence movements, were normal.

Smooth horizontal following movements were present with dissociation occurring only in far lateral gaze. Adduction became deficient, and the abducting eye displayed a slow adducting movement followed by a slow, but faster, abducting movement for 1 or 2 beats. The speed of this abducting movement was slower than that of a normal saccadic movement (less than 400°/s). Only 2 of the 4 affected animals responded to optokinetic stimuli consistently, and the response resulted in an exaggeration of the dissociated movements. Cold caloric stimulus induced dissociation of the fast phase movements in all 4 animals. One animal with ptosis and mydriasis could not generate saccades to the left.

It is of particular interest that 2 of 4 animals with INO demonstrated an asymmetrical pupillary constriction during the adducting phase of nystagmus in the abducting eye. This constriction was greater in the abducting eye. During the abducting phase a corresponding asymmetrical pupillary dilatation took place.

Electromyographic recordings consistently demonstrated the following abnormalities: (1) Delayed inhibition of the medial rectus muscle of the abducting eye in all four of the animals with INO (Figs. 1 and 2); (2) failure of inhibition of the lateral rectus muscle of the abducting eye in 3 of the 4 animals (Figs. 1 and 2); and (3) occasional intermittent excitation of the medial rectus muscle of the abducting

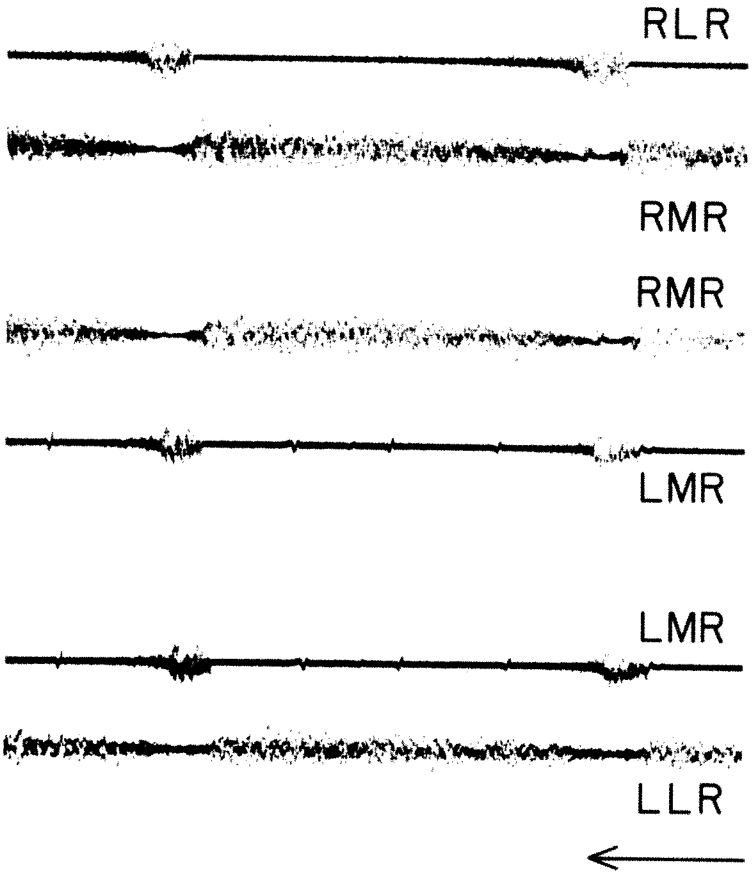

Fig. 4 *The following findings are demonstrated in saccadic movements to the right:*
(1) Partial failure of inhibition of the left lateral rectus;
(2) delayed inhibition of the right medial rectus muscle; and
(3) co-firing of the right medial rectus muscle during an abducting nystagmoid movement
(RLR—right lateral rectus; RMR—right medial rectus; LMR—left medial rectus; LLR—left lateral rectus)

eye, associated with observable abducting nystagmus was seen in all four animals (Figs. 3 and 4). These findings were absent in the remaining animal.

In three of the animals with INO histological studies for the most part showed a clean vertical separation of the two longitudinal fasciculi from the inferior olive to just rostral to the sixth nerve nucleus (Fig. 5). The cut tended to extend deeper at the most caudal end of the lesion, becoming more superficial and fading rostrally. Damage to the MLF was limited to its most medial border, and in two of these cases there was no MLF damage visible from just caudal to the level of the abducens nuclei up to the rostral end of the lesion (Fig. 6).

Discussion

While the lesions certainly did not interrupt all of the nerve fibres concerned with any of the eye movements studied, the disturbed movements observed are a clue to the role of the nerve fibres in the damaged area.

In two of the animals that developed INO after a midline dorsal ponto-medullary lesion, the MLFs were uninjured throughout their course in the pons. The only lesions of the midline were in the medial portion of the MLFs in the medulla. Since all the pathologically documented clinical, as well as experimentally produced, cases of INO had lesions above the medullary level, these lower lesions are presumed not to be responsible for the abnormalities of ocular movement observed in our animals. It appears that a single midline lesion at and about the level of the abducens nuclei separating both MLFs, but not involving either one, can produce bilateral INO. This INO is assumed to be due to the interruption of fibres crossing from one side of the brainstem to the other as originally postulated by Cogan *et al.* (1950) and as demonstrated anatomically after MLF lesions producing INO in monkeys by Carpenter and McMasters (1963), as well as Carpenter and Strominger (1965).

If the interruption of fibres crossing the midline produces INO, then some of these fibres should

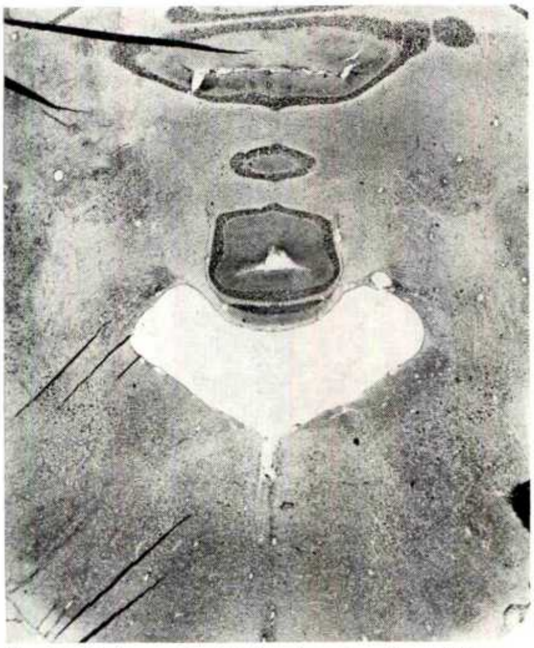

Fig. 5 *Bodine stain of obliquely cut section of the brainstem demonstrating a superficial lesion extending ventrally from the fourth ventricle. There is some damage to the left medial longitudinal fasciculus (× 10)*

control ocular adduction. That such a crossed pathway exists was demonstrated in monkeys by Bender and Weinstein (1944). The nuclei of origin of these fibres has been placed in the vestibular nuclei (McMasters *et al.*, 1966; Carpenter and Strominger, 1965) and in the reticular formation (Szenthagothai, 1961). These fibres cross to the contralateral MLF at the level of the abducens nuclei (McMasters *et al.*, 1966; Carpenter and McMasters, 1963) so that lesions of the MLF above this region produce an ipsilateral weakness of adduction.

The remaining component of INO, abducting nystagmus, has been the subject of varied explanations. These include the interruption of doubly-crossed excitatory pathways to the medial rectus subnucleus (Pola and Robinson, 1976), loss of excitatory input to the contralateral abducens nucleus (Carpenter and McMasters, 1963; Carpenter and Strominger, 1965), and the utilisation of convergence movements in an attempt to compensate for the weakness of adduction (Stroud *et al.*, 1973, 1974). The results of our study lend support to two of these explanations.

Pola and Robinson (1976) postulated that each parapontine reticular formation (PPRF) sends its excitatory and inhibitory fibres into the contralateral MLF and up to both medial rectus subnuclei (Fig. 7). The excitatory fibres were thought to remain on the contralateral side to enter the subnucleus of that side, whereas the inhibitory fibres were presumed to recross the midline to enter the medial rectus subnucleus on the original side of origin. They suggested that during gaze to one side the excitatory and inhibitory commands originating from PPRF on that side are augmented by decreased activity of the opposing contralateral PPRF. In addition they mention that during lateral gaze there are also excitatory and inhibitory signals sent to the motor neurons of each sixth nerve nucleus.

The electromyographic (EMG) findings in INO of Loeffler *et al.* (1966) are difficult to relate to the relatively clean experimental situation. All of their patients had diffuse brainstem disease. Three had evidence of involvement of the area around the third nerve nucleus, and two had failure of conjugate gaze to one side in addition to other signs. In one case that had neither rostral nor caudal involvement they demonstrated a failure of complete inhibition of the ipsilateral medial rectus muscle on conjugate gaze. This muscle also failed to develop appropriate burst activity on attempted contralateral gaze. Electromyographic recordings of our animals with INO

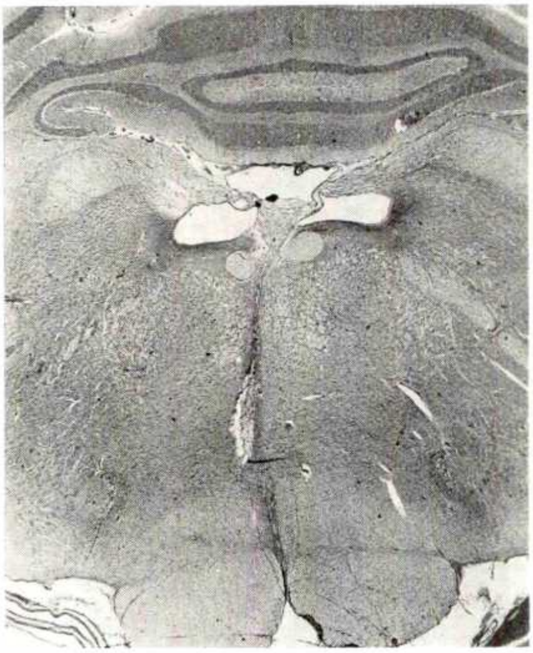

Fig. 6 *Bodine stain of obliquely cut section of the pons demonstrating a lesion extending into the pontine tegmentum with a fibrous ingrowth from the fourth ventricle. The brainstem structures are remarkably intact (× 10)*

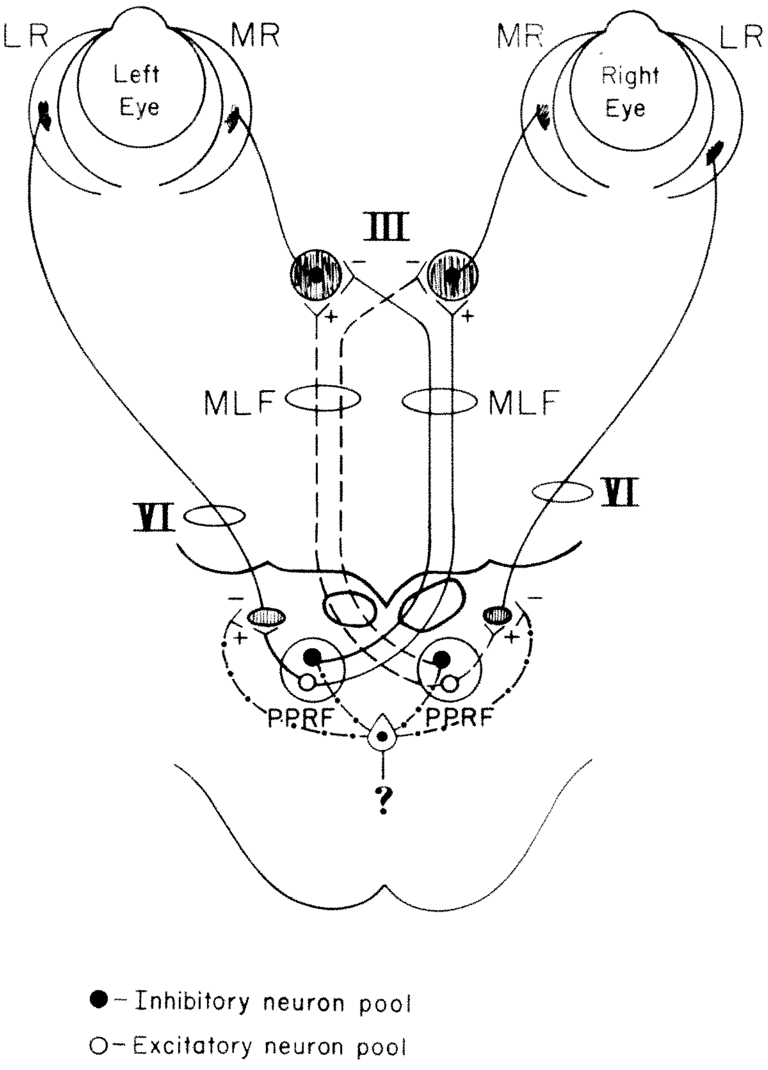

Fig. 7 *LR—lateral rectus; MR—medial rectus; III—third cranial nerve and medial rectus subnuclei; MLF—medial longitudinal fasciculus; VI—sixth cranial nerve and abducens nucleus; PPRF—parapontine reticular formation; +—excitatory; – — inhibitory. Assume a conjugate movement to the left is programmed. Two pools of neurons are activated in the left parapontine reticular formation:* (1) *An excitatory pool sending axons to the left abducens nucleus (VI) and to the contralateral medial rectus subnucleus of the oculomotor nucleus (III) via the MLF; and* (2) *an inhibitory pool sending axons to the contralateral abducens nucleus in a relatively ventral pontine decussation and to the ipsilateral medial rectus subnucleus via the contralateral MLF involving a double decussation. Concomitantly, appropriate pools are inhibited (or excited) in the opposite parapontine gaze centre leading to a further relative facilitation of the agonist and disfacilitation of the antagonist muscle groups involved in the movement (Adapted from Pola and Robinson, 1976)*

demonstrated somewhat similarly delayed inhibition of the medial rectus muscle of the abducting eye. Since the responsible lesion in at least two of these animals is presumed to have been restricted to crossing fibres at the level of the abducens nucleus, these observations lend support to Pola and Robinson's proposal of a doubly crossing inhibitory pathway from a nucleus of origin on one side of the brainstem to the medial rectus subnucleus of the same side.

Neither in their own nor in the clinical studies of INO which they reviewed did Loeffler *et al.* (1966) mention EMG abnormalities of lateral rectus activity. In three of our animals there was lack of normal inhibition of the lateral rectus muscle of the adducting eye but never an abnormality of the abducting eye.

Consequently, we have no evidence to support the hypothesis (Carpenter and McMasters, 1963; Carpenter and Strominger, 1965) that loss of input to the abducens nucleus of the abducting eye is responsible for the abducting nystagmus. The lack of normal inhibition of the lateral rectus of the adducting eye may have resulted from interruption of either of two sources of nerve fibres to the abducens nucleus: fibres crossing the midline at the level of the abducens nuclei (Carpenter and McMasters, 1963; McMasters *et al.*, 1966) or fibres ascending from the vestibular nuclei in the MLF. However, these latter fibres do not enter the MLF until they ascend to the level of the abducens nuclei (McMasters *et al.*, 1966), and consequently, injuries to the MLF below this level would not be expected to affect ocular motor activity. The animal with INO which did not display the inhibition of the adducting lateral rectus had an extremely superficial lesion at the level of the abducens nucleus, suggesting that the fibres involved cross somewhat ventrally.

The occasional intermittent burst of EMG activity in the antagonist medial rectus of the abducting eye was always associated with nystagmus of that eye. This burst was seen only in the two animals that demonstrated pupillary constriction with the adducting movement. Unfortunately pupillary constriction and this electromyographic pattern were never studied simultaneously. However, the EMG recordings do suggest that with each burst of activity in the antagonist medial rectus there is an accompanying increase in the firing of the opposite medial rectus (Figs. 3 and 4). If such an increase in activity of both medial recti were associated with the observed pupillary constriction, this would indicate activation of asymmetric convergence as suggested by Stroud *et al.* (1973, 1974). The electromyographic pattern, here represented by burst activity, is compatible with the activity previously reported in asymmetric convergence by Miller (1959).

Though the dissociated nystagmus seen in our animals was most easily induced by cold caloric stimulation, pupillary changes were only noted in two animals and were associated with abducting nystagmus. This was unlike patterns of pupillary constriction and dilatation seen by DeSantis and Gernandt (1971), who observed an initial marked pupillary dilatation to vestibular stimulation (air jet directed at the utricle) with superimposed rapid minor constrictions of random frequency.

Our experiments suggest that it is possible to produce a deficit in extraocular movements having the characteristics of clinical bilateral inter-nuclear ophthalmoplegia without damage to the medial longitudinal fasciculi. The symmetry of the induced ocular motor dysfunction makes precise statements about eye velocity impossible with the comparative frame technique we have used previously (Burde *et al.*, 1975). In spite of this our observations lend supportive evidence to the schema of Pola and Robinson (1976) which postulates the existence of doubly decussating inhibitory fibre pathways in conjugate gaze movements and to their explanation of the abducting nystagmus of INO (Fig. 7). However, our finding of co-firing of the contralateral medial rectus, as well as the association of the adducting phase of nystagmus with pupillary constriction, is also consistent with the proposal of Stroud *et al.* (1973, 1974) that an asymmetric convergence mechanism is responsible for the abducting nystagmus.

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Optic nerve glioma and phaeochromocytoma associated with von Recklinghausen's disease: A case report

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SUMMARY A 32-year-old woman who died suddenly during pregnancy as a result of an adrenal phaeochromocytoma also suffered from von Recklinghausen's disease. 21 years earlier she had an optic nerve glioma successfully removed. The association between von Recklinghausen's disease and optic nerve glioma/phaeochromocytoma is well established. So far as is known, the present case is the first ever published with the triad: von Recklinghausen's disease, optic nerve glioma, and phaeochromocytoma.

During a follow-up study concerning orbital tumours in childhood (Eldrup-Jørgensen and Fledelius, 1975), we became acquainted with the story of a female who died during pregnancy 21 years after successful removal of an optic nerve glioma. The patient further suffered from von Recklinghausen's disease and died as a result of an adrenal phaeochromocytoma. To our knowledge this clinical triad has not been previously reported.

Case report

In 1964 a 32-year-old pregnant woman was admitted to hospital as an emergency case. After a few hours at home with pain in chest and shoulders she became comatose. Cardiac arrest soon followed, and resuscitation efforts, continued in hospital, were ineffective. At necropsy a large adrenal phaeochromocytoma with a central haemorrhage was found (Fig. 1*a*).

She had experienced throughout her life frequent periods of illness, and been admitted many times (about 20) to various hospitals. In the following account her history is arranged according to symptom groups rather than to chronology.

Von Recklinghausen's disease. The patient's mother and two brothers had café-au-lait spots. Since birth, the patient had had a soft swelling at the left angle of the mouth, which was regarded as primarily a lymph- or haemangioma. During 1939–43, when she was 7 to 11 years old, she received radiotherapy, without effect. During 1948–55 repeated excisions and plastic repair were carried out. Histopathological examination of removed tissue showed neurofibroma. Café-au-lait spots and cutaneous nodules (some of which were pigmented) occurred all over the trunk and limbs, increasing in number with age.

Optic nerve glioma. At the age of 10 she developed protrusion and blindness of the left eye (the right eye remained unaffected throughout life). In 1943 a thickened orbital part of left optic nerve was excised (Krönlein procedure). The pathological report stated it was an optic nerve glioma (oligodendroglioma); signed Erna Christensen, Eye Path. Lab. No. 51/43 (Fig. 1*b*). In the following 21 years there were no signs of local recurrence.

Other neurological symptoms. A brother died at 9 of epilepsy. Since 1954 (aged 22) the patient had had epileptiform attacks (grand-mal type). She was twice examined in a neurological department (1955 and 1962) without findings indicating intracranial tumour or other focal lesion. Treatment was with phenytoine and mysoline. In 1954 she had a head injury with concussion. Since then she has had bifrontal headache almost daily, sometimes with prodromal hemicraniform visual disturbances.

Abdominal symptoms. Since her first pregnancy in 1953 (normal delivery of a normal girl) she has had repeated 'biliary colic', without, however, laboratory or *x*-ray confirmation. Her body weight has always been low (about 44 kg, height 158 cm), sometimes with periods of weight loss. In 1960 an explorative laparotomy disclosed nothing abnormal except small cystic ovaries.

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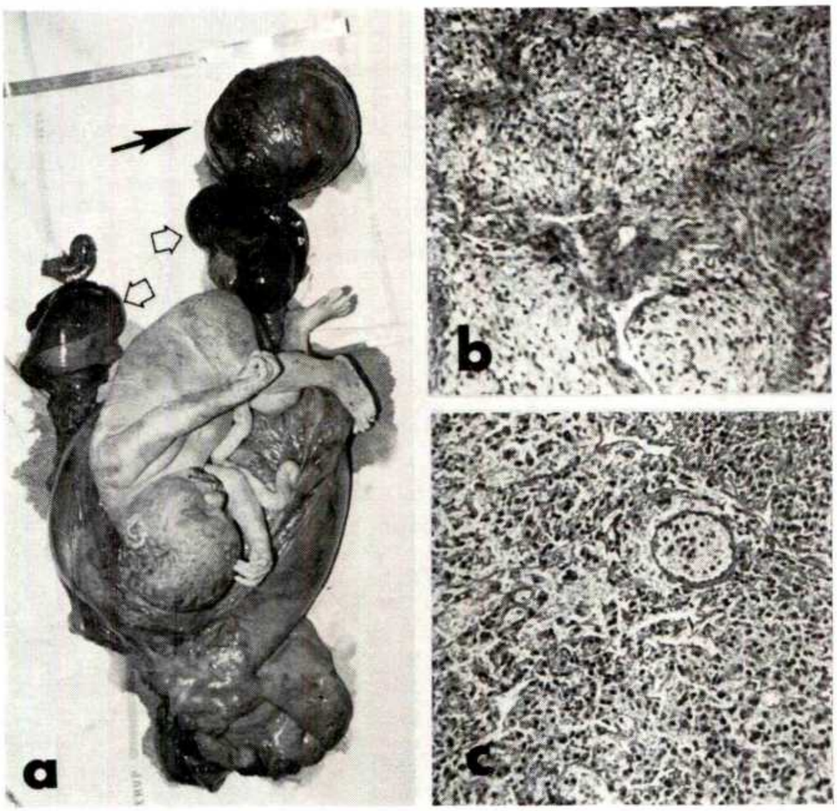

Fig. 1 (a) *Post-mortem photograph of the genitourinary tract showing the female fetus in the uterine cavity.* Above, *the normal kidneys* (white arrows), *the normal right adrenal gland, and the left-sided adrenal phaeochromocytoma* (black arrow). (b) *Histological section from the optic nerve glioma removed 21 years before death (×100).* (c) *Histological section (post-mortem) from the phaeochromocytoma shown in* (a) *(×100)*

Symptoms or findings consistent with a hormone-releasing phaeochromocytoma. No real proof is available because her urine was never examined for vanillyl mandelic acid (VMA) and catecholamines, but the following (possibly related) symptoms appeared: from 1962 frequent episodes of shaking, and sometimes also dizziness and vomiting; later, attacks of palpitations and profuse sweating. Among the findings importance can be attached only to the blood pressure readings recorded during the various admissions to hospital. All were normal except for slight elevations on three occasions: 1960, 180 mmHg systolic during anaesthesia and laparotomy; 1962, 140/100 mmHg in the neurological department; 1964, 150/90 mmHg when admitted for imminent abortion in the second month of her last pregnancy.

Necropsy (J. V. Thorborg)

The main finding was an adrenal tumour (Fig. 1*a*, *c*). At the site of the left adrenal gland an encapsulated mass (14×13×12 cm, weight 300 g) was easily detached from the kidney and other surrounding tissue. On the cut surface a thick peripheral rim of greyish-red solid tumour tissue was observed around a central irregularly torn cavity filled with partly coagulated blood, escaping under pressure when cut. Remnants of the right adrenal gland could be discerned as a 2·5-cm-long slightly prominent ridge on the surface of the tumour.

Histopathology. The sparsely vascularised tumour tissue (Fig. 1*c*) consisted of massive aggregates of fairly uniform cells with rounded or polyhedral nuclei and abundant, slightly granular cytoplasm. Mitoses were not observed. The overall impression from the nuclear morphology was that of a benign tumour. There were some sinusoids and irregular spaces between the cell cords. Chromaffin granules within the tumour cells could not be demonstrated (potassium dichromate stain), probably because of the lapse of time (23 hours) between death and tissue fixation. The diagnosis was phaeochromocytoma with haemorrhage.

Other relevant findings. (a) Positive: The heart (300 g) showed a slight hypertrophy of the left ventricular walls (17 mm in thickness). The spleen was slightly enlarged (500 g). The uterus contained a female fetus (*cf.* Fig. 1*a*), developed according to the duration of the pregnancy and without deformities. *(b)* Negative: The right adrenal gland and the thyroid and parathyroid glands were normal. There were no focal lesions in brain or brain stem, and in particular no tumours, aneurysms, or other vascular malformations.

Discussion

In this rather mixed clinical picture von Recklinghausen's disease must be considered the basic disorder. This disease is known to involve potentially every part of the central and peripheral nervous systems (Crowe *et al.*, 1956), and the symptomatology varies accordingly. Von Recklinghausen's disease is one of the so-called phakomatoses or neurocutaneous syndromes (the other clinical entities usually included being von Hippel-Lindau disease, tuberous sclerosis, and Sturge-Weber's syndrome), a group of often heredofamilial disorders. It is confined to neuroectodermally derived structures, and the additional finding of phaeochromocytomas in some of these patients is not surprising for they develop from neural crest derived tissue (Chapman *et al.*, 1959; Russel and Rubinstein, 1971). To give an idea of the associations of the different disorders in this field the following points from the literature are given in brief (we disregard here the association with thyroid and parathyroid tumours as well as other possible 'neurocristopathies'—*cf.* Bolande, 1974):

Von Recklinghausen's disease. The incidence among the general population is estimated at 1 per 2000 to 3000 (Marshall, 1954; Crowe *et al.*, 1956).

Optic nerve glioma. The incidence of this tumour, mostly confined to childhood, is not given in the textbooks on the subject. Danish material suggests an incidence of about 1 per 100 000 of the population (Christensen and Andersen, 1952; Eldrup-Jørgensen and Fledelius, 1975).

Phaeochromocytoma. The frequency is estimated at 0·05 to 0·1% among the general population, but higher (1%) in selected samples with hypertension (Melmon, 1968; Hansen, 1975).

Phaeochromocytoma and pregnancy. Blair (1963) reviewed 51 cases. Almost half of the women died from the tumour, which was named 'the great mimic', invariably leading to suspicion of pre-eclamptic toxaemia. It appears that the stress of pregnancy and/or the mechanical changes caused by the enlarged uterus may act as a trigger for a pre-existing, previously silent phaeochromocytoma. The same conclusions arose from a more recent review (Schenker and Chowers, 1971) comprising 89 cases; in 39% the phaeochromocytoma was diagnosed only at post-mortem examination. In retrospect, however, there had been recognisable clinical symptoms of phaeochromocytoma in almost all these cases.

Von Recklinghausen's disease and optic nerve glioma. 10 to 40% of patients with optic nerve glioma show evidence of von Recklinghausen's disease (Davis, 1940; Marshall, 1954 *inter al.*). Conversely Crowe *et al.* (1956) found 2 histologically proved optic nerve gliomas in a series of 223 patients with von Recklinghausen's disease (0·9%), but in addition there were several cases of blindness without surgery and histological confirmation.

Von Recklinghausen's disease and phaeochromocytoma. Neurofibromatosis is seen in 4 to 20% of patients with phaeochromocytoma (Glushien *et al.*, 1953; Crowe *et al.*, 1956; Barbeau, 1957; Hume, 1960). Conversely, however, only 1 case of phaeochromocytoma occurred in the above-mentioned series of 223 neurofibromatosis cases (Crowe *et al.*, 1956). This apparent discrepancy was explained, according to the authors, 'by the fact that individuals with phaeochromocytoma may well be rarer than those exhibiting neurofibromatosis'. This explanation, however, is not consistent with the fairly equal frequencies of the diseases cited above.

Associations between phaeochromocytoma, brain tumours, and neurocutaneous disease. Tumours of brain and brain stem were found in 6 out of 223 patients with von Recklinghausen's disease (Crowe *et al.*, 1956). Phaeochromocytoma and optic nerve glioma were *not* reported among the findings in a review of 49 cases of von Recklinghausen's disease with acoustic neurinomas and multiple meningiomas (Rodriguez and Berthrong, 1966). Brain tumours in patients with von Recklinghausen's disease *and* phaeochromocytoma were reported by Barnard and Lang (1964) (disseminated astrocytic gliomas in brain and brain stem) and by Roberts (1967) (cerebral gliosarcoma). The coincidence of phaeochromocytoma and intracranial haemangioma (in a woman, and later also in her son) was reported by Chapman *et al.* (1959), by Chapman and Diaz-Perez (1962), and by Mulholland *et al.* (1969), but there was no cutaneous evidence of neurofibromatosis. Glushien *et al.* (1953) and Vilhelmsen and Fischer (1973) published cases (3 and 1, respectively) of phaeochromocytoma associated with Lindau's disease (intracranial haemangiomas, predominantly cerebellar).

So far as is known the present is the first published case with the clinical triad of von Recklinghausen's disease, optic nerve glioma, and phaeochromocytoma. As an additional point, it may be added that the adrenal tumour caused the patient's death during pregnancy. Furthermore, the prevailing neurological symptoms (epilepsy, headache, etc.) might have been caused by intracranial manifestations of von

Recklinghausen's (or Lindau's) disease. The examinations performed (PEG, repeated EEG's) did not, however, reveal focal pathology, and lesions could not be demonstrated at brain necropsy. Her epilepsy should therefore be considered as heredofamilial and/or part of a post-concussion syndrome.

Earlier reports of sudden death due to massive haemorrhage into adrenal phaeochromocytomas (Lehman and Rosof, 1956; Huston and Stewart, 1965) emphasised abdominal pain and a state of shock as prevalent features. These also occurred in our patient, who did not die in a state of hypertension as is usually seen in lethal phaeochromocytomas. In relation to our patient the case of Lehman and Rosof (1956) was of further interest because of the necropsy finding of 'a small meningioma in the area of the optic chiasm'. There was, however, no (other?) evidence of von Recklinghausen's disease.

The special interest of the present case is the coincidence of an inter-relationship between von Recklinghausen's disease and phaeochromocytoma. With this in mind the vague and neurasthenic type of complaints of the patient might have led to a suspicion of a phaeochromocytoma as a possible cause of her symptoms in the last 2 years of life. It is not unusual for patients with phaeochromocytoma to be found normotensive for years and to have only slight symptoms. For example, Hermann and Mornex (1964) in a study of 507 reported phaeochromocytomas noted that 10% were clinically latent. In some of these the tumour was disclosed by the unexpectedly severe responses to usually harmless examination procedures or—as in our case—to pregnancy.

Except for early treatment of the optic nerve glioma ophthalmologists were concerned in the present case only as consultants. The lesson for ophthalmologists is that they should be alert for optic nerve tumours and orbital neurofibromata in patients with von Recklinghausen's disease, and also look carefully for vascular retinal lesions. Hypertensive angiopathy may point to phaeochromocytoma, and retinal angiomas may be part of von Hippel-Lindau disease.

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British Journal of Ophthalmology, 1977, **61**, 244–245

Operating microscope eyepiece heaters

A. P. W. MAKEPEACE AND J. C. DEAN HART
From the Departments of Medicine and Ophthalmology, University of Bristol

SUMMARY Precipitation of water vapour from expired air on to exposed eyepiece lenses of operating microscopes can seriously interfere with the surgeon's view. By warming these optical surfaces to temperatures well above the dew point of expired air this problem is eliminated. A pair of small heaters were designed to clamp over the eyepiece tubes of a standard operating microscope and their effectivity assessed.

Water vapour condensation on exposed eyepiece lenses of operating microscopes is more likely to occur at critical periods during surgery because of involuntary alterations of the operator's breathing patterns. The vapour pressure of end expired air exhaled through the mouth is greater than that expressed through the nares because of the air-conditioning role of the turbinates. Prolonged use of adhesive tape to fix surgical face masks to surrounding skin, thus deflecting expired air away from eyepiece lenses, may give rise to skin irritation. Antimisting preparations applied to such optical surfaces provide only a temporary protection against condensation, but warming of the eyepieces to temperatures well above the dew point of expired air will eliminate this problem.

A pair of small heating elements was therefore designed to fit over the eyepiece tubes of a standard operating microscope and their effectiveness assessed.

Apparatus

The heating elements consist of 2 blocks of aluminium alloy which have been drilled out to accommodate 2 small resistors. The blocks are clamped over the eyepiece tubes and fixed by tightening a screw. When in position the heaters do not interfere with the surgeon's view and the mobility of the microscope is unimpaired (Fig. 1). With a power supply of 3·6 W to each element, derived from the light source of the microscope, temperatures at the centre of the exposed eyepiece lenses, the eyepiece tube, and the heaters were recorded before switching on the power supply and subsequently at 12 and 48 minutes.

Results

The eyepiece lenses become sufficiently warm 12 minutes after the heaters are activated to prevent clouding of the operator's view even when the optical surfaces are breathed upon directly. 36 minutes later the temperature of the eyepiece tube is raised by only a further 4°C (see Table 1). At this

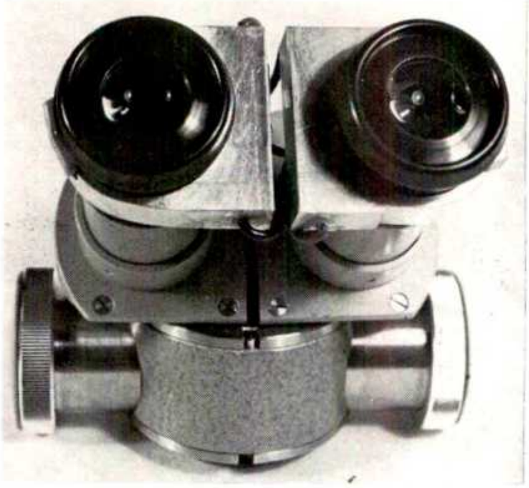

Fig. 1 *Eyepiece heaters on operating microscope*

Table 1 *Temperature recordings*

Time (minutes)	*Temperature (°C)*		
	Centre of lens surface	*Eyepiece tube*	*Heaters*
0	22	22	22
12	33	36	41·5
48	36·5	40	46

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time a steady state is reached, as the mass of the microscope acts as an effective heat sink.

Comment

Although it is possible to achieve higher initial temperatures by increasing the power rating, sensing devices would then need to be incorporated into the design of the apparatus to prevent subsequent overheating. With the apparatus described the time required to raise the temperature of the eyepiece lenses sufficiently above the dew point of expired air is not unduly great. As the power is derived directly from the electrical supply to the microscope light source, the twin objects of safety and simplicity of design are achieved.

We wish to thank the Department of Medical Illustration, University of Bristol, for photographic services, and Mrs M. Roach for secretarial help.

British Journal of Ophthalmology, 1977, **61**, 246–247

A moving-mirror gonioscope for retinal surgery

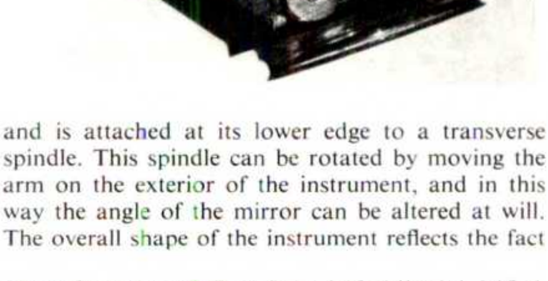
DAVID OWEN
London

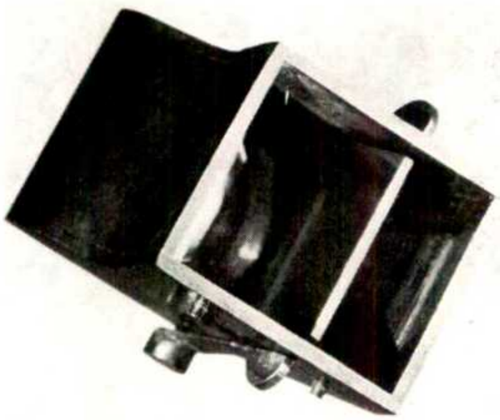
SUMMARY A moving-mirror gonioscope for use in retinal surgery is described, and its advantages are discussed.

The advantages of the use of the operating microscope in surgery of the anterior segment of the eye are well known. To attempt to gain these advantages in surgery of the retina and vitreous must involve the use of a contact lens to neutralise the curvature of the cornea. In addition provision must be made to allow examination of the periphery of the fundus. This paper describes a new instrument designed to fulfil these purposes.

Description

The contact lens consists of a plano-concave lens, diameter 12 mm, radius of curvature 7·5 mm, mounted in the base of the instrument. The walls of the instrument, composed of black Perspex, enclose an air-filled space, in which is mounted the single movable mirror. The mirror is rectangular in shape, and is attached at its lower edge to a transverse spindle. This spindle can be rotated by moving the arm on the exterior of the instrument, and in this way the angle of the mirror can be altered at will. The overall shape of the instrument reflects the fact that only one mirror is used, and is designed to minimise obstruction to the surgeon. The roof of the instrument is formed by a thin rectangular sheet of Perspex, but this functions merely as a dust-cover, for it is removed when the instrument is in use.





Use

The instrument is designed to be used in theatre on the anaesthetised patient. The pupil must be fully dilated. Lid retractors or sutures are used in the usual way, and the instrument is placed on the cornea. To avoid air bubbles a jet of saline from a syringe is directed just beneath the instrument as it is lowered on to the cornea, a manoeuvre which is not difficult to accomplish. The surgeon continues to hold the instrument in contact with the cornea, the most convenient grip being with the thumb and middle finger, thus allowing the index finger freedom to adjust the angle of the mirror by pushing the lever on the exterior of the instrument backwards or forwards as desired. This procedure takes a little practice.

The surgeon then adjusts the microscope to obtain a view of the fundus. A slit beam is required,

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with its axis just a few degrees off the viewing axis, and the surgeon finds the optimum arrangement in exactly the same way as in the case of the Goldman three-mirror lens. The motorised traversible slit illuminator of Carl Zeiss, Oberkochen, is excellent for this purpose, and an X-Y coupling mechanism is also most helpful.

The surgeon's free hand may be used to indent the sclera, for which purpose finely-toothed forceps are convenient. It is sometimes necessary to alter the position of the instrument relative to the eyeball a millimetre or two, and, in practice, it is found easier to keep the instrument still and rotate the eyeball beneath it by means of toothed forceps gripping the episcleral tissues (the same forceps being used for indentation).

The periphery of the fundus is examined by directing the slit beam on to the mirror of the instrument, and a more anterior or a more posterior view in that particular meridian is obtained by adjusting the angle of the mirror. With indentation the ora serrata and pars plana may readily be seen, and with the mirror as far back as it will go the angle of the anterior chamber may be examined. Different meridians are examined merely by rotating the instrument on the globe. The sense of continuity thus achieved is very helpful to the surgeon in orientation and in the interpretation of what he sees. The optic disc and posterior pole can be examined by directing the beam straight through the contact lens, i.e., in front of the lower edge of the mirror.

Discussion

The advantages of contact lens biomicroscopy over other methods of examination of the fundus have been described elsewhere (Goldman, 1949; Schirmer, 1970). The chief advantages are the greater magnification afforded, the greater information a strong slit beam provides, especially in respect of three-dimensional appreciation, and a reduction of the effect of scatter from opacities of the media as compared with coaxial illumination. The use of an instrument with a single adjustable mirror avoids the loss of continuity which results from the use of an instrument with multiple fixed mirrors. Frisen (1972) has described an ingenious instrument incorporating one fixed and one adjustable mirror. The instrument described here, however, has been designed specifically for use in the operating theatre in the hope that it will enable the operating microscope to be more effectively used in retinal surgery.

I am much indebted to Mr G. Nissel and company, and to Mr M. Ruben and the contact lens department, Moorfields, for constructing the prototypes. I am also most grateful to Mr A. G. Bennett, of City University, for much helpful advice on the optics of the instrument.

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Obituary

Sir Allen Goldsmith, KCVO, MB, BS, FRCS, 1909–1976

Everyone who knew him personally and many of those who knew him by repute will be sad to hear of the death of Allen John Bridson Goldsmith on 13 December 1976, shortly after his 67th birthday.

The son of a doctor, Bridson K. Goldsmith, he was born in India on 27 November 1909, and on the family's return to their ancestral home in the Isle of Man he was initially educated at King William's College on that island. Thereafter his career in medicine was brilliant. He entered the Middlesex Hospital, London, in 1928, graduated MB, BS with distinction in medicine and pathology in 1931, and, maintaining his high academic standards, became demonstrator in physiology, senior Broderip scholar and Lyell gold medallist, went through the house posts, and acted as assistant pathologist at that hospital, taking the FRCS in 1934. He then went to Moorfields Eye Hospital, where he was a house surgeon and resident medical officer from 1935 to 1937 and pathologist and curator from 1937 to 1940. At the same time (1937) he was elected surgeon and pathologist to the Central London Ophthalmic Hospital and the Paddington Green Children's Hospital (1937–46). Being unfit for military service owing to tuberculosis, he joined the Emergency Medical Service (1939–45). In 1946 he was appointed ophthalmic surgeon to the Middlesex Hospital, and on the amalgamation of the Central London with Moorfields Eye Hospital he was appointed surgeon to the Holborn Branch of that hospital in 1948, where he worked until 1958, when he retired to devote all his attention to the Middlesex Hospital, his spiritual home, which he served unremittingly and with affection, becoming a governor in 1957. Other hospitals whereon he served were the Royal National Orthopaedic and the King Edward VII Hospital for Officers. He acted as the honorary secretary of the ophthalmological section of the Royal Society of Medicine (1941–3) and of the Ophthalmological Society of the United Kingdom (1950), becoming vice-president (1968–71); he was an examiner in ophthalmology for the royal colleges in 1948 and was also a vice-president of the Medical Defence Union. He was appointed surgeon-oculist to HM Household in 1952, receiving the CVO in 1962, and became surgeon-oculist to the Queen in 1965, receiving the KCVO in 1970.

With all these activities he conducted a large private practice. His thorough training in medicine and pathology made him a clinician of outstanding ability, a fact widely recognised throughout the profession. He had a remarkable facility for keeping abreast of recent advances in his specialty and was adept in applying them in his clinical activities; moreover, he was an unusually competent and successful surgeon. Withal, he was an eminently kindly and considerate person, at the same time gentle and completely honest. By his patients he was adored; to them he was not only a doctor but also an understanding friend. To his colleagues and on committees his quiet wisdom and solid principles combined with unusual modesty made him invaluable.

Unfortunately, throughout his life he was dogged by ill health, which curtailed his activities more than he liked. He was forced to retire completely in March 1976, when he went to his country home in Kent, and it is sad that throughout his retirement he was never well up to the time he died. His death is sincerely mourned both by his colleagues and by his patients. He married in 1936 Mabel Rosemary Elise Porter, the daughter of a doctor, and left one son and two daughters. To them and to his widow we all extend our heartfelt sympathies.

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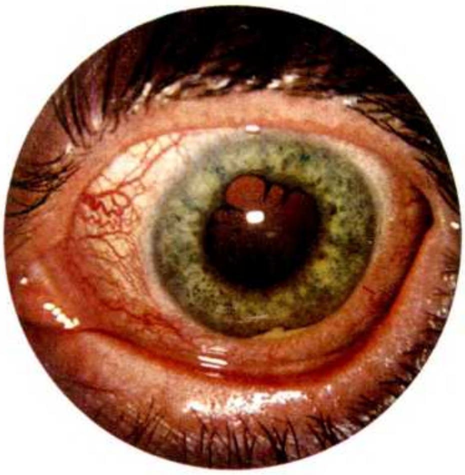

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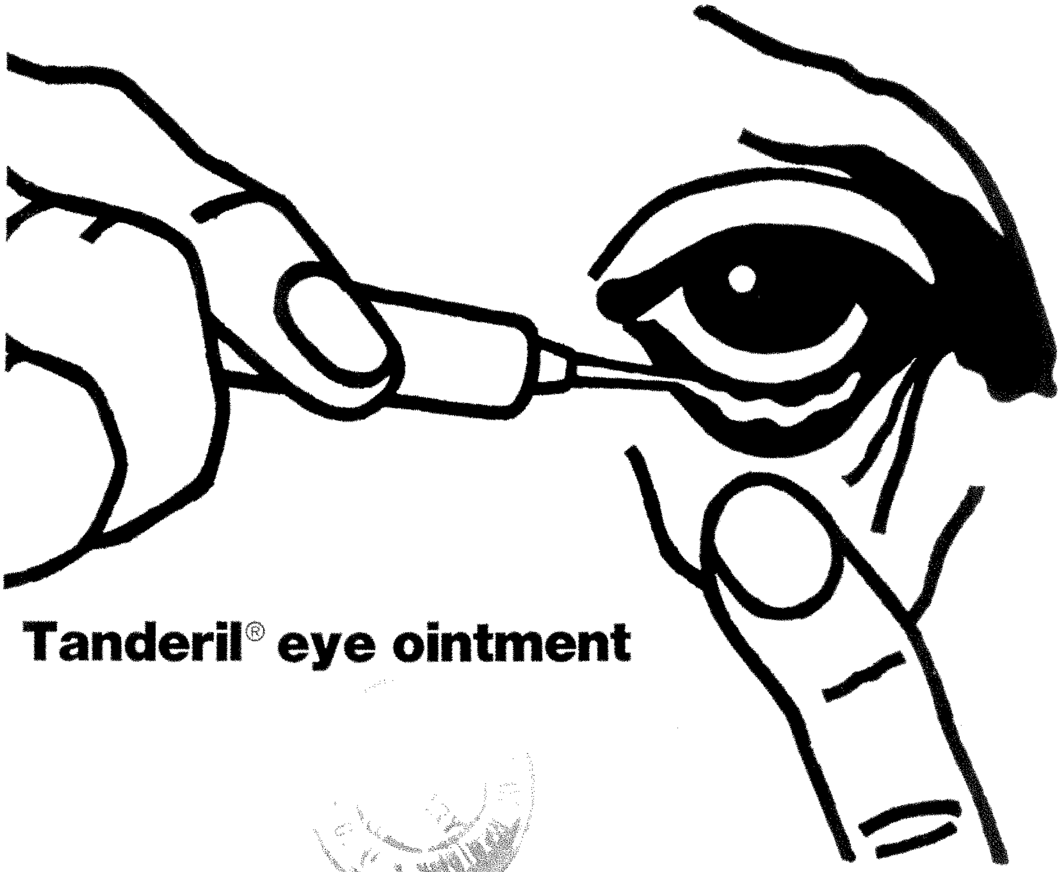

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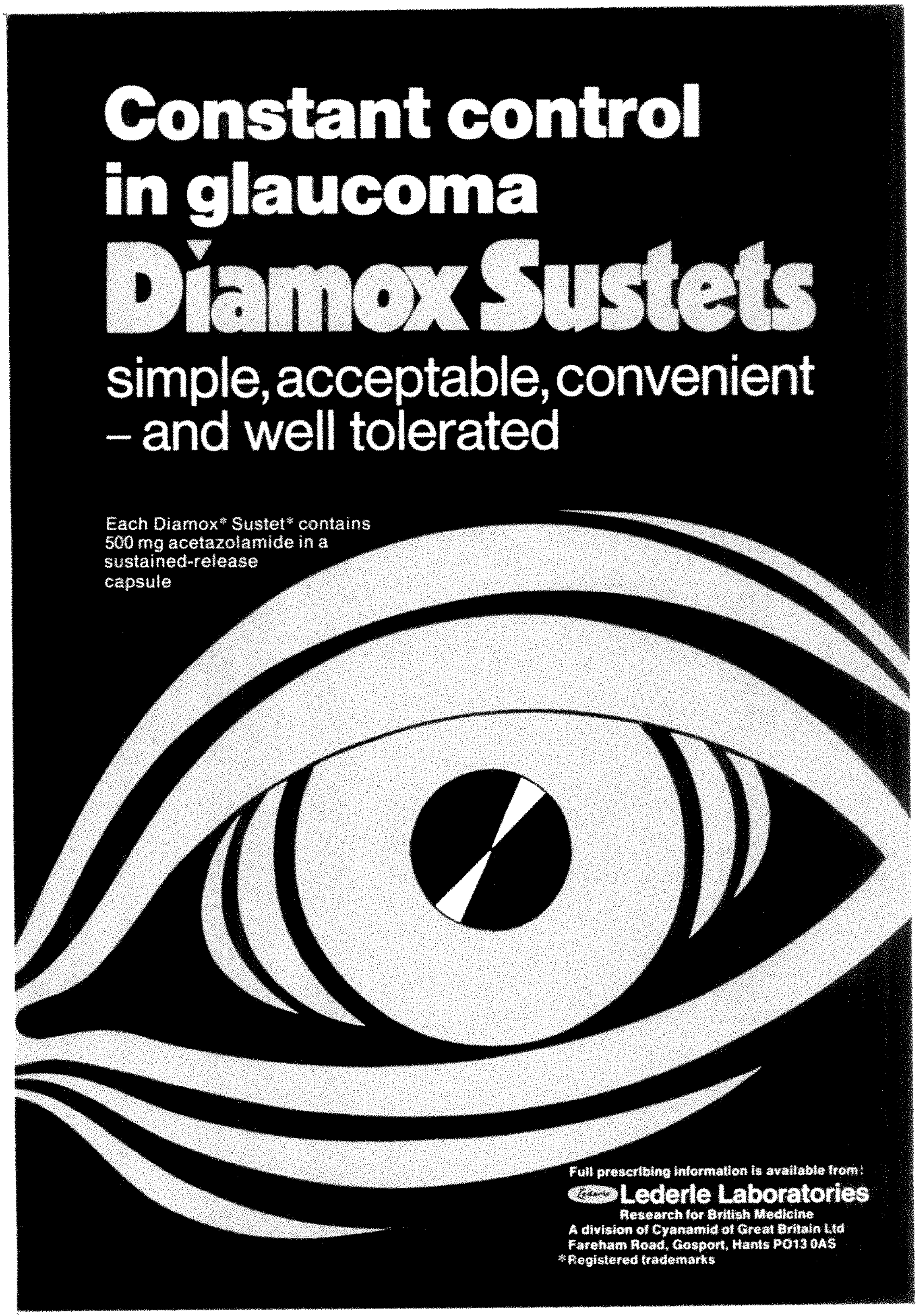

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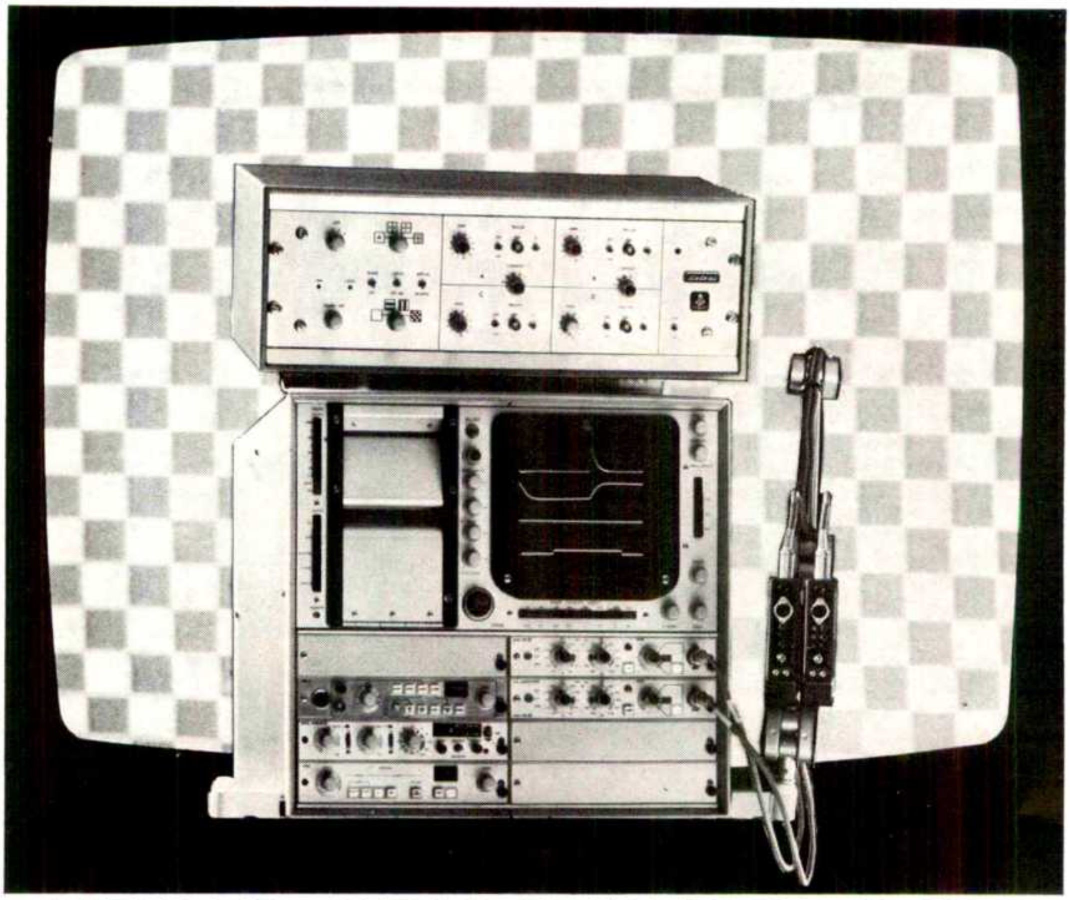

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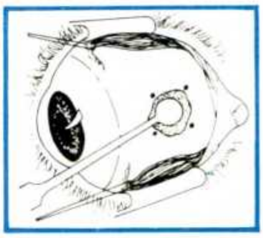

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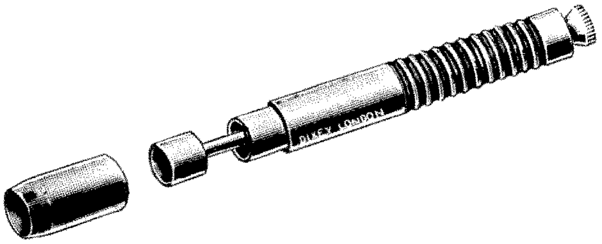

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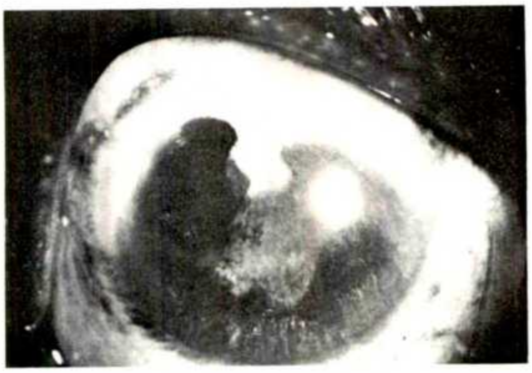

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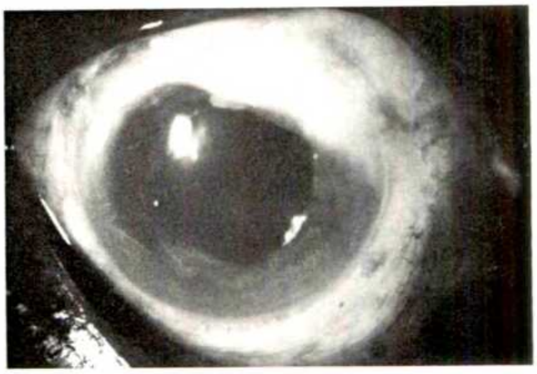

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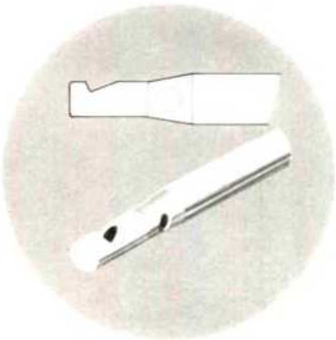

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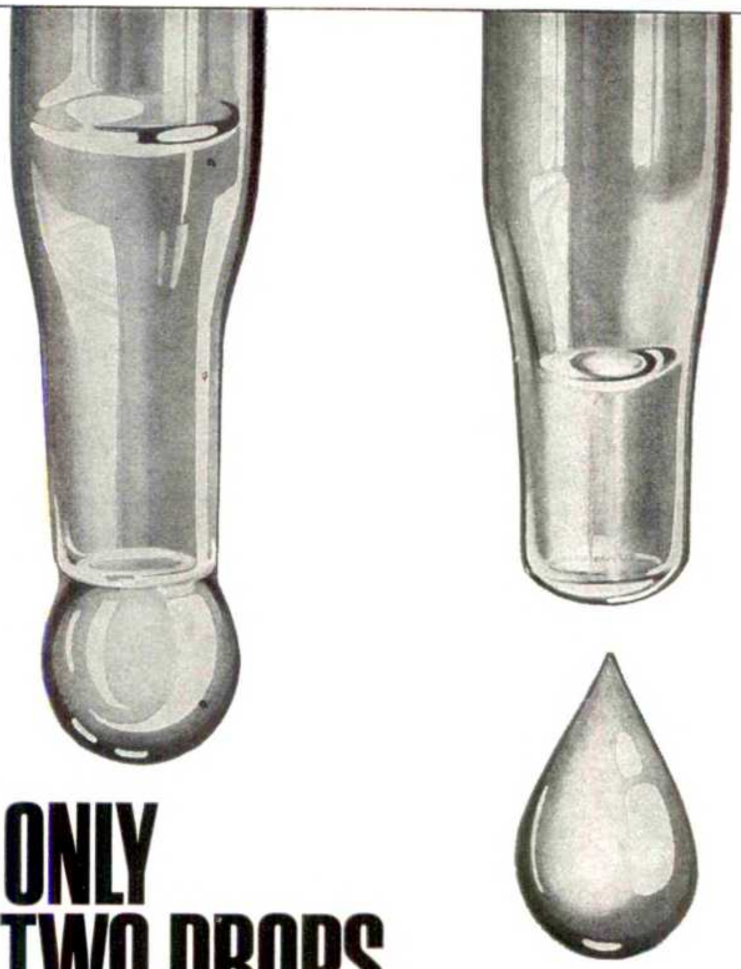

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Editorial: Infection with contact lens wear

In this issue R. L. Cooper and I. J. Constable report several instances of corneal infection related to prolonged wearing of soft contact lenses. More than one type of lens material was used, and the wearing periods varied but were all within the pattern now known as constant wear or extended wear. This period can be logically taken to mean anything more than 24 hours, but in practice is often much longer. For each patient the lens material and the number of days before the lens has to be removed are often not related. This report is not isolated. Ruben (1976) reported an incidence of corneal infection in contact lens wear as determined by hospital outpatient reports and concluded it was higher for soft-lens wearers. The same author also reported in a well-controlled series of daily-wear patients with low refractive error using heat disinfection that no infection occurred over a year of observation.

There is no mechanism at present for reporting eye infection due to contact lens wear, and therefore accurate assessment of the problem is impossible. Nevertheless, corneal infection in a contact lens wearer who for all intents and purposes has normal eyes is a serious matter. Permanent severe loss of sight from contact lens wear should not occur, though one must expect a higher incidence in patients with abnormal eyes who require contact lenses or prosthetics, some of whom may be prone to recurrent eye infection. The latter group are under the supervision of the medical practitioner, and the side-effects of treatment are often anticipated and controlled when they occur.

The pertinent question to be asked by the practitioner who is responsible for the care of the general puplic wishing to wear contact lenses is, Can infection of the cornea be completely avoided?

The regimens for the control of pathogens likely to infect the contact lens, its solutions, and container have been described in several papers, both for hard and soft lenses. The BSI, Australian Standards, FDA, and, more recently, the Working Party on Contact Lens Preparations Draft Report for the UK Department of Health have either published or have in draft form proposals for the licensing and control of preparations used in conjunction with contact lenses and likely to be the source of infection. But it is evident that irrespective of the quality, efficiency, and safety of preparations that the wearer of contact lenses uses there remains the problem of his failure to comply with instructions and the manufacturer's or practitioner's ignorance of the elements of hygiene. This has resulted in some non-medical practitioners thinking that cold sterile saline by itself will disinfect a lens or keep a lens and case sterile.

But apart from the introduction of pathogens on to the eye from faulty technique in handling and disinfecting a lens there remains the variable factor that at one instant the corneal and other superficial eye tissue may be within normal limits, and at the next a foreign body or imperfect lens may inflict trauma or anoxia which may result in cell oedema and necrosis and predispose an eye to infection. The public will be protected more in the future from materials and lenses and solutions likely to have a toxic effect on their eyes. The practitioner should advise the individual intending to wear lenses for long unsupervised periods of the conditions likely to enhance infection and toxic reactions of the eye, and that a problem does exist. The manufacturer who advises lenses for specific purposes, such as permanent wear, must ensure that the lenses and preparations used with the lenses provide a safe system as tested by laboratory and clinical trials by reputable teams of workers. Provided manufacturers, practitioners, and patients take all precautions, there is little risk of eye infection from the sensible use of contact lenses. But where a contact lens has a proved risk of infection, whether because of its material, fitting, method of disinfection and cleaning, or period of wear, the authorities and the patient must be so advised. It is accepted practice that a surgical or medical treatment has to be explained to the patient as to the benefits, complications, and failure rate before a patient agrees to treatment. Likewise a patient must be informed about the risks of constantly wearing contact lenses before beginning.

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British Journal of Ophthalmology, 1977, **61**, 250–254

Infective keratitis in soft contact lens wearers

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SUMMARY Eight cases of infective keratitis are reported in wearers of soft contact lenses. Four of them had normal eyes and were wearing lenses on a continual basis. One was wearing a lens continually for therapeutic reasons. Three others were wearing lenses daily or intermittently. The four latter cases were using contaminated lens solutions. Two of the continual lens wearers lost vision to the point of blindness. A significant factor in their bad outcome was the fact that both lived in areas remote from adequate ophthalmic services.

Serratia liquefaciens was implicated in one case. This is thought to be the only reported case of corneal abscess due to this organism in the past 16 years. *S. marcescens* was grown in another case from the lens solutions and carrying case.

The introduction of the soft contact lens with improved patient tolerance and ease of fitting has led to rapid increase in its use both for therapeutic and optical indications. The high oxygen transfer of the 70 and 85% water content lenses has prompted the use of constant wear in some centres. In view of the widespread use of soft contact lenses it is surprising how few reports of complications in normal eyes have accumulated in the literature. This is a report of 8 cases of infective keratitis associated with soft contact lens wear, mainly in normal eyes, with both daily intermittent and constant wear.

Case summaries

Infection with constant wear soft lens for optical indications

Case 1. A 78-year-old female from a remote town presented with a 3-day history of painful red right eye. She had worn a Sauflon 70% water content constant wear lens for unilateral right aphakia for 2 years, and visited her contact lens practitioner every 3 months 350 miles from home for lens cleaning.

On examination visual acuity was right eye 6/24 with the contact lens, 6/12 left with spectacle correction. There was a right purulent conjunctivitis with 2 central superficial corneal abscesses. Corneal scraping culture grew *Pseudomonas aeruginosa*. She responded well to local tetracycline and systemic carbenicillin, with minimal residual scarring and visual acuity of 6/18.

Eight months later with continued wearing of the right contact lens she presented again with the same history and vision in the right eye reduced to hand movements. At this admission there was 1 central superficial corneal abscess and a severe haemorrhagic iritis with marked fibrin exudate in the anterior chamber of the right eye. Culture from the corneal scrapings grew *Serratia liquefaciens* from enrichment media. She responded favourably to intensive gentamicin and steroid therapy, which left her with a corneal nebula. The contact lens was not worn again. Visual acuity in that eye recovered to 6/18 with aphakic spectacle correction.

Case 2. A 29-year-old male had been wearing soft contact lenses for 5 years. No record of the type has been obtainable. For 12 months before admission wear was continuous.

He was admitted after 1 week's history of a painful red right eye. Vision was perception of light right eye and 6/36 left eye without correction. There was a large central full-thickness right corneal abscess with minimal peripheral corneal oedema (Fig. 1). No growth was obtained on culture. Very slow and incomplete healing occurred over 6 weeks on amphotericin B and gentamicin subconjunctival injections, with systemic amoxycillin, gentamicin, and Probenecid. He took his own discharge. Visual acuity 1 year later was 6/24 without correction. A small central corneal scar remained.

Case 3. A 23-year-old female had been wearing an 85% Sauflon contact lens continuously for 2 years for simple myopia when she developed a painful red left eye 2 days before admission. Visual acuities were 6/24 right, and hand movements left

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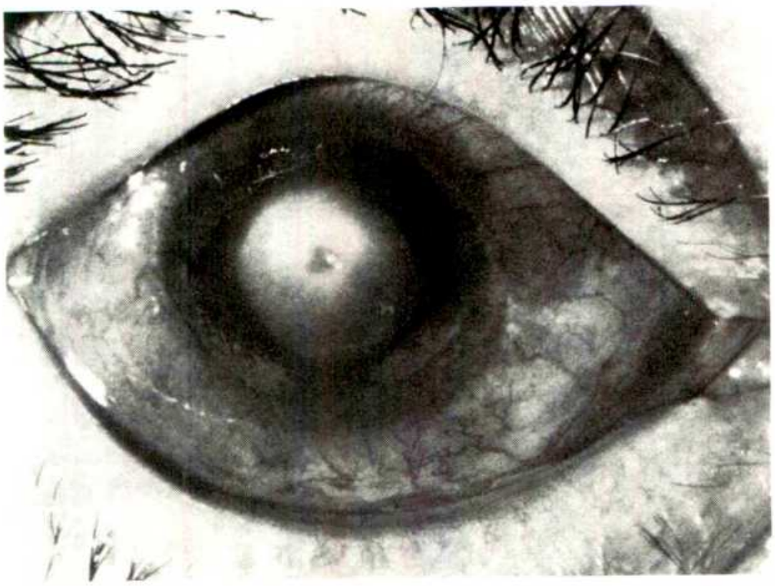

Fig. 1 *Photograph of case 2. Large central full thickness corneal abscess due to continual wear of soft contact lens*

without correction. Six superficial yellow/white abscesses were scattered across the centre of the left cornea (Fig. 2). They involved the epithelium and Bowman's membrane and were surrounded by considerable oedema. Several marginal yellow abscesses were also noted along the superior limbus. There was a 1 mm left hypopyon, with fibrin occluding the pupil. In both eyes 10 to 12 midstromal leashes of new vessels extended 2 mm into the corneae from the limbus. Scrapings and culture grew *Staphylococcus aureus* from the left eye.

Treatment with 1 subconjunctival injection of gentamicin sulphate 20 mg was followed by continuous infusion of gentamicin sulphate 3 mg/kg per 24 hours in normal saline, delivered at a rate of approximately 1 drop every minute into the superior conjunctival fornix. The end of a thin Silastic tube, as used for canalicular intubation, was

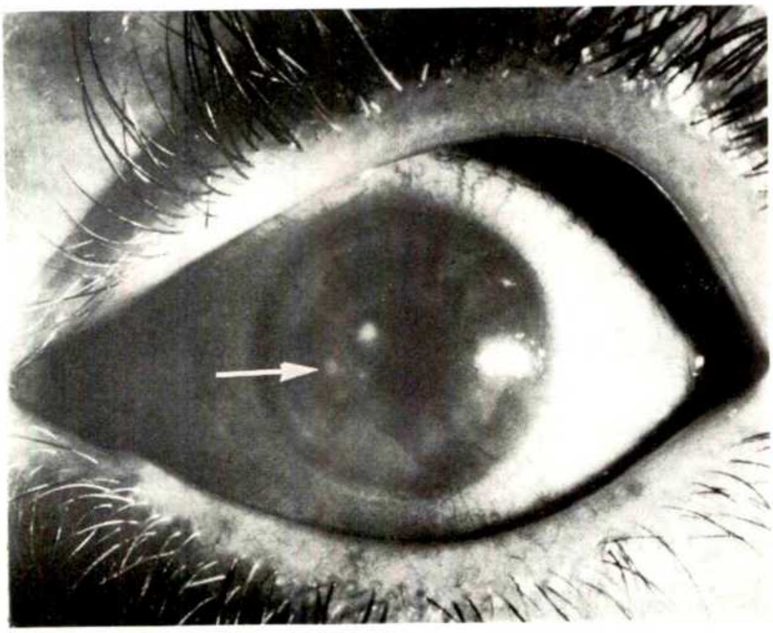

Fig. 2 *Photograph of case 3. Central superficial corneal abscesses* (arrow) *due to continuous wear of soft contact lenses*

placed in the upper fornix. The tubing was glued to the cheek and temple with Dow Corning silicone rubber adhesive. (Medical Grade 'Adhesive B'.) A fine butterfly needle was introduced into the distal end of the tubing and an intravenous giving set attached to the infusion bottle.

The abscesses healed in 4 days, at which time the infusion was stopped. Corrected visual acuity in the left eye was 6/12 after 4 weeks. No further follow-up was possible.

Case 4. A 19-year-old female from a remote town presented with 1 week's history of a painful red eye, the onset of which was 1 day after a swim in a muddy river. She was wearing Hydron lenses constantly for myopia. For 3 days before admission she was treated with Soframycin eye drops, and systemic Tobramycin.

On admission vision right 6/9, vision left hand movements. There was a large sloughing left central corneal ulcer surrounded by stromal oedema. Cultures for herpes virus, bacteria and fungi were unrewarding. No organisms were found on microscopy. Despite treatment with subconjunctival framycetin and amphotericin B and local nystatin a hypopyon developed after 5 days. This cleared rapidly over the ensuing 10 days and the ulcer healed. She was left with a dense central stromal scar and vision of 3/60 in the affected eye. She continues to wear a right soft lens and has after 2 years had a successful penetrating left keratoplasty.

Infection with constant lens wear for therapeutic indication

Case 5. A 78-year-old female was prescribed a Sauflon 85% lens for treatment of bullous keratopathy (Fuchs's combined dystrophy) of the right eye. Six days after fitting the lens and shortly after pouring a cleaning solution into the eye she experienced severe burning pain. (She had been instructed to do this regularly each day by her contact lens practitioner.) On examination visual acuities were 6/60 right with the lens and 6/18 left with spectacle correction. She had a purulent conjunctival discharge, moderate epithelial irregularity, and stromal oedema.

Cultures of the conjunctival discharge and the lens solution both grew *Enterobacter aerogenes*. She responded rapidly to local gentamicin and chloramphenicol. The eye remains irritable from her bullous keratopathy, and no change in visual acuity has occurred. Contact lens wear has not been resumed.

Infections with intermittent and daily wear for optical indications

Case 6. This 24-year-old nurse was wearing a 70% water content Sauflon soft contact lens for about 12 to 16 hours a day for myopia (−8·00D.S.). About 4 months after starting their wear she developed a painful right eye. She removed both lenses for 4 days and then reinserted the left lens. She rapidly developed pain in the left eye. On admission vision was 6/6 right eye, 6/60 left eye with glasses. She was found to have a healing right paracentral corneal ulcer, and 2 small paracentral superficial left corneal ulcers with 1 mm left hypopyon. Culture from the left corneal ulcers yielded no organisms. However, culture of the solution used for cleaning the lens grew *Pseudomonas pyocyanea* and *Escherichia coli*. She responded well to subconjunctival injections of gentamicin, local chloramphenicol, and systemic amoxycillin. She no longer wears contact lenses and has 2 small superficial paracentral nebulae in the left cornea, and 1 paracentral right nebula. Visual acuities are 6/9 right, 6/12 left with spectacle correction.

Case 7. A 56-year-old male intermittently wore optical cosmetic Sauflon soft contact lenses. Not having worn the lenses for 4 months, he inserted the right lens directly from a 4-month-old sterilising solution without resterilising the lens. After about 4 hours he developed severe pain in the right eye.

On examination visual acuity was 6/18 right, 6/9 left with glasses. There was a 1 mm superficial paracentral corneal abscess, folds in Descemet's membrane, and marked flare and cells in the anterior chamber. Gram film of the corneal scrapings showed Gram-negative rods, which proved to be *Escherichia coli* on culture. The contact lens solution grew *Enterobacter aerogenes* and *Pseudomonas* species.

Response to treatment, initially with amphotericin B and specifically with gentamicin locally, was rapid. The central abscess healed, leaving a small residual subepithelial nebula, and 6/9 vision, corrected, in that eye.

Case 8. A 19-year-old female had been wearing Hydron soft contact lenses occasionally for 3 months when she developed a painful red left eye. She had inserted the lens in the eye after a break in wear of 2 weeks without again rendering the lens aseptic, and had wet the lens with Normal saline before insertion. Visual acuity was 6/12 right, 6/36 left, without correction. An area of fine punctate epithelial keratitis was visible in the upper half of the left cornea, with minimal fluorescein staining. There were fine keratic precipitates and a faint flare. Cultures grew *Staphylococcus albus* from the conjunctiva and *Serratia marcescens* from both contact lens solutions and the carrying case. She responded well to removal of the lens and local chloramphenicol drops. After 1 month she resumed wearing the soft contact lens. Final visual acuity in the affected eye was 6/9.

Table 1 *Infective keratitis associated with continuous wear of soft contact lenses*

Case no.	*Age*	*Sex*	*Indication*	*Lens type*	*Duration of wear*	*Organism*	*Final acuity*
1*a*	78	F	Unilateral aphakia	Sauflon 70%	2 years	*Pseudomonas aeruginosa*	6/12 With contact lens
1*b*	78	F	Unilateral aphakia	Sauflon 70%	2 years 8 months	*Serratia liquefaciens*	6/12 With glasses
2	29	M	Optical	Not known	1 year	None, presumed mycotic	6/60 at 5/12 Dense scar
3	23	F	Optical (myopia)	Sauflon 85%	2 years	*Staph. aureus*	6/12 With glasses
4	19	F	Optical (myopia)	Bausch & Lomb	3 months	None, presumed mycotic	3/60 Dense scar
5	78	F	Therapeutic bullous keratopathy	Sauflon 85%	6 days	*Enterobacter aerogenes*	No change

Five of the above cases of infective keratitis wore soft contact lenses continuously, 4 prescribed for optical and 1 for therapeutic indications (Table 1). Of the patients with normal eyes 1 was aphakic: she had no filtering blebs or loose sutures to account for her infection, and had 2 episodes of corneal abscess. Two of the patients were blind after healing, 1 of whom has had a successful penetrating keratoplasty. Both of these patients lived in remote areas and were referred late to ophthalmic services. One of them went swimming in a muddy river immediately before the infection while wearing the contact lenses. The patient wearing the therapeutic lens was using a contaminated irrigating solution.

The second group consisted of 3 patients wearing soft lenses on a daily or intermittent basis (Table 2). The cause of the keratitis in 2 of these patients was failure to render their lenses aseptic after a period of 2 or more weeks between insertions. All 3 patients had contaminated lens solutions and carrying cases.

Discussion

The literature was reviewed from 1956, from which year several reports were made of infective keratitis and even endophthalmitis occurring in hard contact lens wearers with normal eyes (Payrau and Perdriel, 1956; Heydacker, 1956; Lansche and Lee, 1960; Nauheim, 1962; Fitzgerald *et al.*, 1962; Dixon *et al.*, 1966). Two reports were found of infections due to trauma to filtering blebs by hard contact lenses (Wild, 1962; Ashline and Ellis, 1968). Only 2 reports were found of infective keratitis occurring in normal eyes wearing soft contact lenses on a daily or intermittent basis (Thomson, 1973; Ruben, 1976) and one in constant wear soft lenses for optical indications (Ruben, 1976).

However, several reports have been made of this complication in abnormal eyes wearing therapeutic soft lenses on a continual basis (Brown *et al.*, 1974; Dohlman *et al.*, 1973; Dohlman, 1974; Ruben, 1975). In 1 report of punctate epithelial keratitis in continual soft lens wearers for optical indications no infective aetiology was suggested for this complication (Brown and Lobascher, 1975). Infection in 30% of continual wear soft lenses for optical indications has been reported, but keratitis was not mentioned in this context (Benson, 1976).

Studies of the conjunctival flora of hard and soft lens wearers have shown no significant differences

Table 2 *Infective keratitis associated with daily and intermittent wear of soft contact lenses*

Case no.	*Age*	*Sex*	*Indication*	*Lens type*	*Wear pattern*	*Eye*	*Solutions*	*Final acuity*
6	24	F	Optical (myopia)	Sauflon 70%	16 hours per day for 4 months	None	*Pseudomonas aeruginosa*, *E. coli*	6/9 RE 6/12 LE (corrected)
7	56	M	Optical	Sauflon	Occasional for 2 years	*E. coli*	*Pseudomonas*, *Enterobacter aerogenes*	6/9 (corrected)
8	19	F	Optical	Hydron	Occasional	*Staph. albus*	*Serratia marcescens*	6/9 With contact lens

from non-lens wearers until, in the case of soft lens wearers, the lenses have been worn for more than 6 months (Kapetanski *et al.*, 1964; Winkler and Dixon, 1964; Tragakis *et al.*, 1973).

In our series of constant wear lenses for optical indications cases 1, 2, and 3 had no predisposing factors and had worn the same lenses for more than 6 months (Table 1). Benson (1976) does not give a minimum period of time for his infected cases. The predisposing factor for infection in case 4 was a swim in a muddy river while wearing her lenses. Case 5 in the continual wear group, and each of the intermittent lens wearers reported, highlight the well-known risks of contamination of lens solutions and storage cases (Table 2). Unlike the hard lens wearers, the soft lens wearer cannot store his lenses in a dry, well-ventilated carrying case for his protection (Winkler and Dixon, 1964).

The organisms isolated in our series have all been reported previously as being contaminants of lens solutions, or normal conjunctival flora, apart from *Serratia liquefaciens* (case 1*b*) This organism caused a severe haemorrhagic iritis and a superficial corneal abscess. *Serratia marcescens* (case 8) has been implicated in causing keratoconjunctivitis, corneal abscess, or ulcer (Lazachek *et al.*, 1971; Atlee *et al.*, 1970; Tokunaga *et al.*, 1969), and has recently been cultured from patients wearing soft lenses continuously and from their wetting and storage solutions (Benson, 1976). Case 3 showed signs suggestive of mycotic keratitis, and although it was not proved microbiologically there was a dramatic improvement with amphotericin B.

Predisposition to infection in contact lens wearers is thought to be due to abnormalities of the epithelium induced by poor oxygenation (Brown and Lobascher, 1975). However, evidence of abnormal metabolism like that induced by minimal trauma, including depletion of glycogen stores and ATP, has been found in animal eyes wearing contact lenses of high gas permeability (Thoft and Friend, 1975).

It is apparent that continual wear of soft contact lenses should not be prescribed in the normal eye without strict supervision. This endorses the conclusions of Brown and Lobascher (1975). Adequate instructions should be given to patients, preferably in written as well as verbal form. This should cover all types of wear pattern. Particular stress should be placed on the instructions for rendering aseptic the soft lenses and their carrying cases after an interval in wearing. Fresh solutions should be used, and carrying cases should be boilable or capable of withstanding pasteurisation. It is obvious that boiling or pasteurisation of soft contact lenses is preferable to making them aseptic by chemical means because of the dangers of solution contamination. However, the weak li in the chain always lies in the handling of lens with contaminated fingers; hence instruction in th aspect of the lens care is just as important as sterilisation methods. Regular cleaning of soft lens is mandatory, especially before boiling, to preve accretion of denatured mucus, protein, and forei bodies.

This collection of serious infections in patien wearing soft lenses suggests that it is much con moner than published reports would imply. Contr over the sterility of sterilising and cleaning solutio might need to be improved. Patients should be to to report for immediate medical examination if the develop pain or blurred vision while wearin contact lenses.

We thank the surgeons who referred cases and ga permission for publication of cases in their care.

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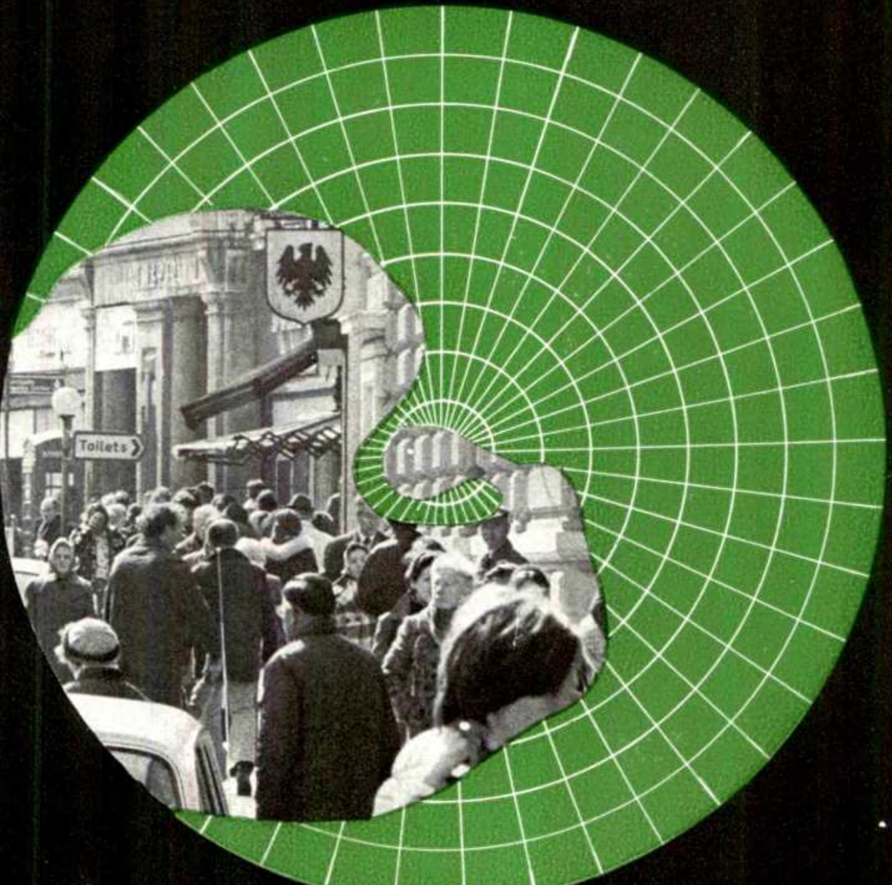

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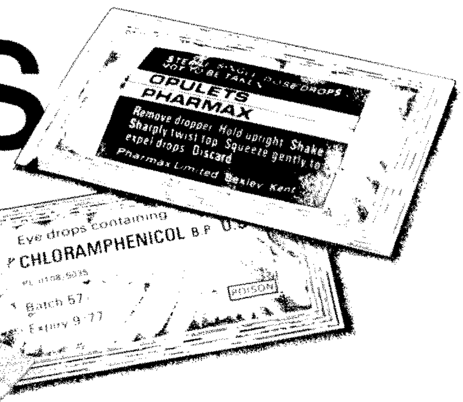

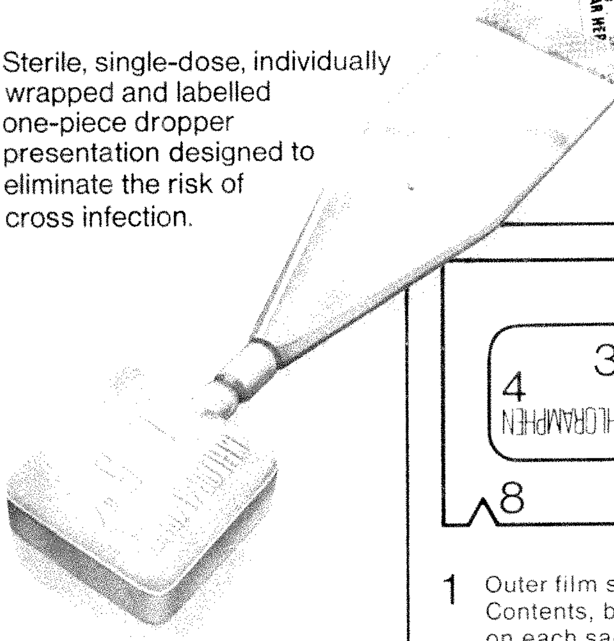

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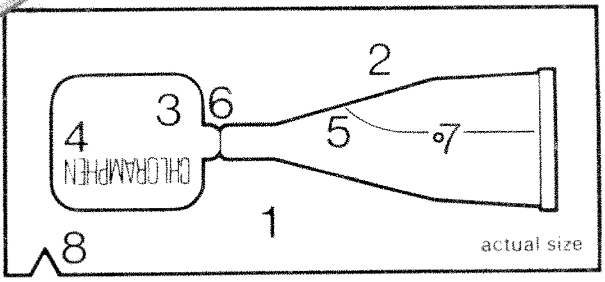

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British Journal of Ophthalmology, 1977, **61**, 255-259

Treatment of TRIC infection of the eye with rifampicin or chloramphenicol

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SUMMARY An open trial was carried out on 63 patients in London to assess the efficacy of 1% rifampicin eye ointment in comparison with 1% chloramphenicol eye ointment in the treatment of sexually transmitted TRIC infection of the eye. Patients included were selected on the basis of positive cultures for *Chlamydia trachomatis*.

Three weeks' treatment with rifampicin eye ointment used 3 times daily was not sufficient to cure the disease, but a 6 or 7 week course gave 90% clinical and microbiological cure rate. Treatment with chloramphenicol eye ointment 3 times daily for 4 to 6 weeks failed to cure the disease.

Rifampicin, a semisynthetic antibiotic, irreversibly inhibits the growth of *C. trachomatis* (i.e., TRIC agents and lymphogranuloma venereum [LGV] agents) apparently by the inhibition of the agent's DNA-dependent RNA polymerase (Becker, 1972; Becker *et al.*, 1970).

A clinical trial in schoolchildren with active hyperendemic trachoma in Southern Tunisia (Dawson *et al.*, 1975a) showed that rifampicin eye ointment twice daily for 10 weeks was substantially more beneficial than boric acid ointment, but it appeared to have no advantages over tetracycline eye ointment.

Several authors have claimed that chloramphenicol topical therapy is effective against trachoma (Choumakov *et al.*, 1951; Leo, 1951; Scuderi and Bellomio, 1952; Vasilieva, 1958). However, we have repeatedly isolated *C. trachomatis* from the eyes of persons with continuing active disease despite treatment with chloramphenicol eye drops or ointment before referral to us.

The purpose of this study was to assess in a carefully monitored open trial, using various regimens of treatment, the efficacy of rifampicin eye ointment in comparison with chloramphenicol eye ointment in the treatment of paratrachoma, i.e., sexually transmitted TRIC infection of the eye.

Subjects and methods

SELECTION OF PATIENTS

The patients included in this study were selected on the basis of positive cultures for TRIC agent from patients with acute follicular conjunctivitis referred to the External Eye Disease Clinic at Moorfields Eye Hospital. Patients who had symptoms of concurrent genital infection were excluded from this study and were referred to the diagnostic clinic for investigation and treatment with oral tetracycline, as were those who were not able to attend for 12 weeks' follow-up.

CLINICAL EXAMINATION

Clinical signs observed with a Haag-Streit 900 slit-lamp and symptoms were recorded on a proforma using an extension of the scoring system used for the study of trachoma (Dawson *et al.*, 1975b). The symptoms and signs were graded on a 0 to 3 scale, as indicated in Table 1. The highest possible score was 92: 12 for symptoms and 80 for signs in any one eye.

LABORATORY INVESTIGATIONS

Conjunctival swabbings collected from different areas of the conjunctiva were placed in plastic capsules containing 2SPS transport medium (Darougar and Jones, 1971) and stored in a liquid nitrogen refrigerator until transported to the laboratory, where they were stored in a refrigerator at -70°C until the time of inoculation. The methods of culture in irradiated McCoy cells and the identification of isolates have been described elsewhere (Darougar *et al.*, 1970), also the method of measuring the antibiotic sensitivity of chlamydial isolates in cell culture (Treharne *et al.*, 1977).

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Table 1 *The maximum scoring value of symptoms and signs observed in TRIC infection of the eye*

Symptoms	*Maximum score*	
Lachrymation	3	
Discharge	3	
Grittiness	3	
Photophobia	3	
Signs		
Bulbar conjunctiva		
Hyperaemia	3	
Limbus		
Oedema	3	
Pannus	5	
Cornea		
Epithelial punctate keratitis	3	
Subepithelial punctate keratitis	3	
Palpebral conjunctiva		
(Scores for each of 3 areas of conjunctiva, i.e., upper tarsus, upper fornix, and lower lid, were recorded separately)		
Hyperaemia	3	
Diffuse infiltration	3	
Papillae	3	
Follicles—area	3	Product 9
Follicles—size	3	
Scar	3	

MEDICATION

Either 1% rifampicin eye ointment or 1% chloramphenicol eye ointment was applied by the patient 3 times daily for a period of 3, 4, 6 or 7 weeks.

FOLLOW-UP INVESTIGATIONS

After the initial clinical and laboratory examination treatment was started, and follow-up examinations, with the collection of specimens, were made at weekly intervals for 4 weeks, then at 6 and 8 weeks, and were continued at 3, 6, 12, and 18 months after treatment.

Results

Sixty-three patients were included in this study. The ratio of male to female was 32:31. The ages of the patients ranged from 10 days to 49 years, but the majority were between 20 and 40 years old.

The allocations of the 63 patients with various syndromes of infection of the eye by *C. trachomatis* to treatment with either rifampicin or chloramphenicol is shown in Table 2.

Chloramphenicol was the first drug to be tested in 4- and 6-week courses.

Rifampicin was given first as a 3-week course. The duration of treatment was then increased from 4 to 6 and 7 weeks for several groups of patients.

CHLORAMPHENICOL TREATMENT

The results of the treatment with chloramphenicol for 4 or 6 weeks are shown in Table 3 and Fig. 1. In general a slight improvement in the clinical signs and symptoms followed the treatment. The average clinical score in patients treated for 6 weeks reduced from 41 to 28 at the end of the treatment. Microbiologically all patients treated for 4 weeks remained positive for *C. trachomatis*. Of those treated for 6 weeks 7 out of 10 were still positive for *C. trachomatis*. The 3 patients with negative culture for *C. trachomatis* at the end of 6 weeks' treatment were still clinically suffering from a moderate follicular conjunctivitis. Because of the activity of the disease and positive cell culture all patients

Table 3 *Number of patients cured following treatment with rifampicin or chloramphenicol eye ointment*

Period of treatment (weeks)	*Chloramphenicol*		*Rifampicin*	
	Clinical	*Microbiological*	*Clinical*	*Microbiological*
3			0/3*	0/3
4	0/7	0/7	4/5	4/5
6	0/12	3/12	26/29	24/29
7			7/7	7/7

*Number of patients cured/Number of patients treated.

Table 2 *Allocation of patients with various ocular syndromes of infection by* Chlamydia trachomatis *to treatment with either rifampicin (R) or chloramphenicol (C)*

Syndrome	*Ophthalmia neonatorum*		*Inclusion conjunctivitis*		*TRIC punctate keratoconjunctivitis*		*Trachoma*		*Totals*	
Drug used	*C*	*R*	*C*	*R*	*C*	*R*	*C*	*R*	*C*	*R*
Weeks of treatment										
3	0	0	0	3	0	0	0	0	0	3
4	0	1	5	1	2	3	0	0	7	5
6	0	6	7	16	4	5	1	2	12	29
7	0	0	0	3	0	4	0	0	0	7
									19	44

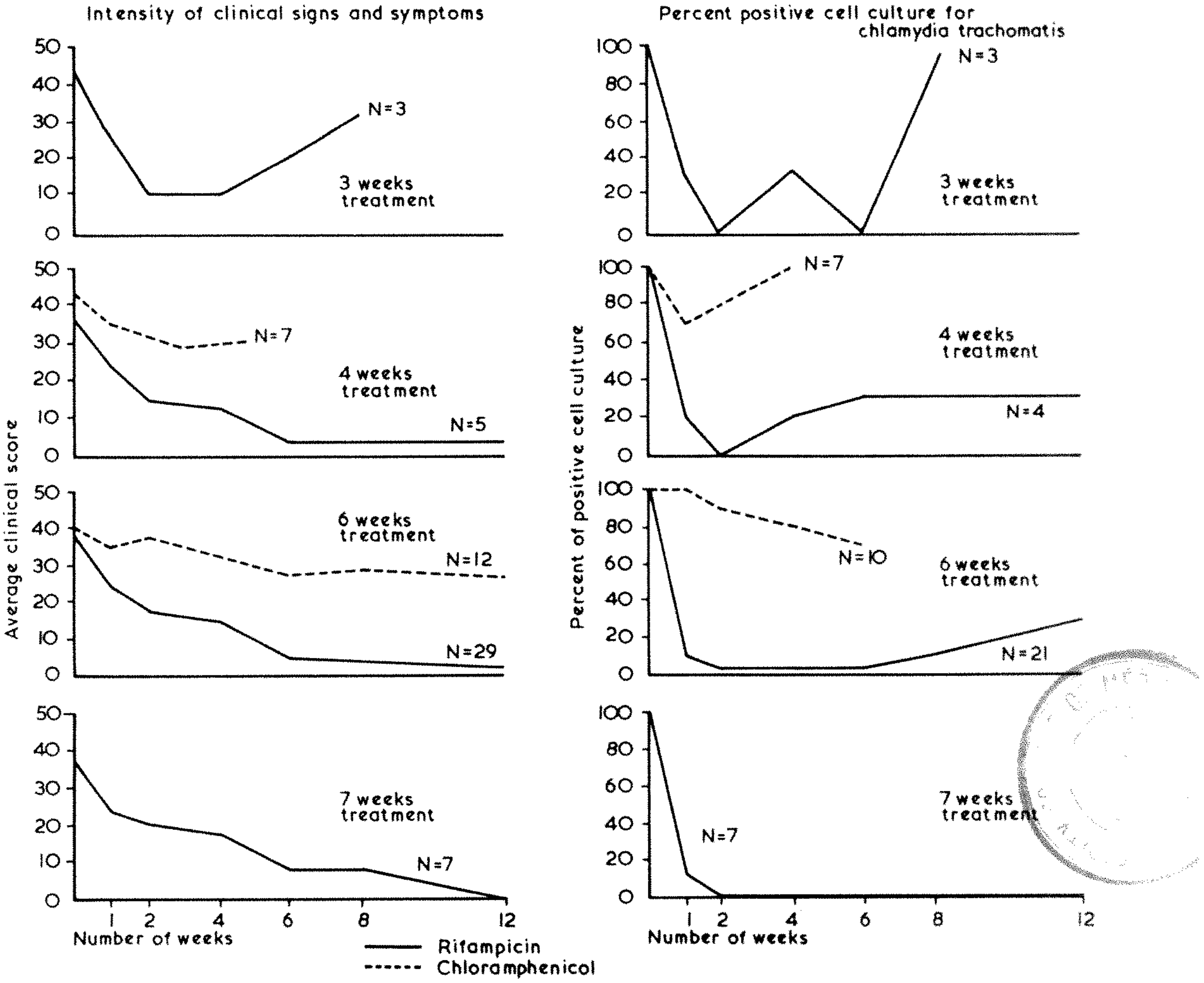

Fig. 1 *Changes in the average clinical score and percent positive cell culture after treatment with rifampicin or chloramphenicol*

except 1 were treated with rifampicin or tetracycline eye ointments. The 1 patient who partially improved during 6 weeks' treatment with chloramphenicol was followed up for 3 months. No changes were observed in his clinical signs and he remained positive for cell culture for *C. trachomatis* until he was treated with tetracycline ointment.

RIFAMPICIN TREATMENT

Three weeks' therapy

The clinical and laboratory findings in 3 patients included in this study are shown in Table 3 and Fig. 1. The average clinical scores before treatment and at 4 weeks after treatment were 43 and 10 respectively, showing a marked improvement in the clinical signs. Microbiologically only 1 patient was positive for *C. trachomatis* at 4 weeks' follow-up. One week later this patient showed an active recurrence of infection and was then cured by a further course of this treatment. The remaining 2 patients showed an increase in the signs of activity in their eyes with an average clinical score of 20 at 6 weeks, increasing to 33 at 8 weeks after the treatment. All 3 had again become agent-positive by the eighth week.

Four weeks' therapy

The result of the treatment of 5 patients with rifampicin eye ointment for 4 weeks is shown in Table 3 and Fig. 1. The average clinical score before the treatment was 37, decreasing to 13 at the end of 4 weeks' treatment. The follow-up observations up to 12 weeks showed no clinical activity in 4 patients. The other patient—an adult with the inclusion conjunctivitis syndrome who was microbiologically positive at the end of 4 weeks—showed a slight degree of activity in her clinical signs at 12 weeks. Two weeks later she developed a moderate recurrence of inflammation with a positive cell culture for *C. trachomatis*.

Six weeks' therapy

The clinical and microbiological findings in 29 patients treated for 6 weeks are shown in Table 3 and Fig. 1. The average clinical scores before and at the end of 6 weeks' treatment were 38 and 5 respectively. The clinical examination of these patients at 12 weeks showed a moderately active disease in only 3 adults, who were originally suffering from inclusion conjunctivitis or TRIC punctate keratoconjunctivitis. The cell culture was positive for *C. trachomatis* in these 3 patients. Two of these received further treatment with tetracycline eye ointment. The third patient, who was followed up for 6 months, showed a moderate follicular conjunctivitis with a positive cell culture during this period. The follow-up investigations in 12 patients over 1 year and 6 patients over 18 months showed no clinical or microbiological signs of infection in their eyes.

Microbiologically at 12 weeks' follow-up 6 out of 21 patients tested were positive for *C. trachomatis*. Of these 6 patients only 3 developed a recurrence of inflammation. The cell cultures from another patient were positive only once at 12 weeks. The clinical and microbiological findings in this patient at 6 and 12 months' follow-up remained negative. The other 2 patients with positive cell culture at 12 weeks were babies with TRIC ophthalmia neonatorum. Although both babies clinically responded well to the treatment, one remained positive for *C. trachomatis* during the treatment and the second baby became positive at 12 weeks' follow-up. The frequent clinical examinations in these babies over 1 year showed no signs of active disease in their eyes, though 1 baby remained positive for *C. trachomatis* for 3 months and the other one for 6 months.

Seven weeks' therapy

In 7 patients who were treated for 7 weeks the average clinical scores before and at 8 weeks and 12 weeks after treatment were 37, 8, and 2 respectively (Table 3 and Fig. 1). Microbiologically all the 7 patients were negative for *C. trachomatis* at 8 weeks' follow-up. In 4 of these patients who were followed for over 1 year the clinical and microbiological investigation remained negative.

Adverse reaction

Three of the 44 patients treated with rifampicin eye ointment developed an adverse reaction 2 to 4 weeks after the start of treatment. This consisted of increased watering soon after application of the ointment, with swelling of the lids together with oedema and increased hyperaemia of the bulbar and palpebral conjunctiva. After treatment was stopped the symptoms and signs subsided in less than 1 week in each case. These patients were removed from the trial. In 4 other patients slight irritation, discomfort, and watering lasting 10 to 50 minutes were reported after each application of the ointment. These patients, however, completed the prescribed course of treatment.

ANTIBIOTIC SENSITIVITY

With an irradiated McCoy cell-culture the minimum concentration that inhibits the development of *C. trachomatis* inclusions was 0·05 μg/ml for rifampicin and 1·0 for chloramphenicol against a variety of *C. trachomatis* serotypes. The minimum lethal concentration of rifampicin or chloramphenicol that inhibits the multiplication of *C. trachomatis* after removal of the drug was 1·0 and 5·0 μg/ml respectively.

In 3 patients who were not cured after a 6-week course of treatment with rifampicin *C. trachomatis* isolates recovered from them before and after the treatment were all shown to be inhibited by 0·05 μg/ml of rifampicin. Thus resistance to rifampicin had not developed in these agents after treatment with rifampicin.

Discussion

In this series of studies we found that after 1 week's treatment with 1% rifampicin eye ointment used 3 times daily the signs and symptoms were markedly diminished and 87% of the 44 previously positive patients became negative for *C. trachomatis*.

Although the number of patients included in the 3-week course of treatment was small, it appears that 3 weeks' treatment is not sufficient for the complete eradication of *C. trachomatis*. Of the patients treated for either 4 or 6 weeks 1 out of 5 and 3 out of 29, respectively, were not cured. There was an initial clinical response to the treatment in these 4 patients, but the inflammation recurred 8 to 12 weeks later. The other 2 patients (babies with TRIC ophthalmia neonatorum) clinically responded well to the treatment, but microbiologically they remained positive for a period of 3 to 6 months. Although there was no obvious default in application of the ointment in these patients, it is possible that these babies may not have received the ointment in their eye according to the instructions.

The long-term follow-up studies (up to 18 months) indicate that thrice daily treatment with 1% rifampicin eye ointment for a period of 6 to 7 weeks can cure the disease in 90% or more of patients with ocular paratrachoma in London.

In a placebo-controlled trial in Southern Tunisia Dawson *et al.* (1975a) have shown that, in the short term, 1% rifampicin eye ointment applied twice daily for 10 weeks markedly benefited severe hyperendemic trachoma.

Several authors have claimed that chloramphenicol topical therapy is effective against trachoma (Choumakov *et al.*, 1951; Leo, 1951; Scuderi and Bellomio, 1952; Vasilieva, 1958). In this study we found that a 4- to 6-week course of treatment with 1% chloramphenicol eye ointment 3 times a day appeared to reduce the severity of clinical signs and symptoms slightly but did not cure the infection nor did it eliminate the *C. trachomatis*. Hence there appears to be no place for chloramphenicol ointment in the treatment of *C. trachomatis* infections

The authors are indebted to colleagues at Moorfields Eye Hospital for referring their patients and to the members of the External Eye Disease Clinic for their collection of clinical specimens and to Lepetit Pharmaceuticals Ltd. for provision of drugs and facilities for laboratory tests.

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Intraocular gentamicin as intraoperative prophylaxis in South India eye camps

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SUMMARY The incidence of bacterial endophthalmitis has been 3·6% after cataract extraction in the eye camps of South India from 1961–75. During this time 50 791 cases were operated using systemic and topical chloramphenicol prophylaxis.

This study evaluated the prophylactic intracameral injection of 50 μg of gentamicin in eye camp cataract extractions. Only 6 of 1626 patients treated with intracameral gentamicin at operation developed bacterial endophthalmitis, an incidence of 0·37%.

While the incidence of endophthalmitis in the well-developed countries has been reduced to acceptable levels of 0·1 to 0·2% (Allen and Mangiaracine, 1964, 1973), the disorder is still one of the major complications after cataract extraction in the developing countries. This has been the case especially in the eye camps in South India, where large numbers of patients (up to 500 per day) are operated on. These eye camps serve the rural masses who cannot afford the expense of coming to a hospital which may be as far as 80 miles (130 km) from their village.

In the past, before the introduction of intraocular gentamicin as prophylaxis against endophthalmitis, each patient was given 250 mg of chloramphenicol by mouth 8 hours before surgery. Chloramphenicol ophthalmic drops were instilled in the eye 1 hour before surgery. Postoperatively the patients were given chloramphenicol 250 mg by mouth every 8 hours and 1% chloramphenicol eye drops were instilled at daily dressing changes.

Additional preoperative medication included 10% phenylephrine and 1% atropine eye drops 1 hour before surgery. In addition to the 250 mg of chloramphenicol 25 mg of chlorpromazine was given orally 1 hour preoperatively. Facial and retrobulbar injections of 1% lignocaine solution were given immediately preoperatively.

The surgeon's and nurse's hands were scrubbed and rinsed with an ether-soap mixture. Operating staff put on sterile gowns, which were used throughout the operating day. Gloves were not worn, all surgery being done with bare hands. The hands were rinsed between cases with sterile water and occasionally washed again with the ether-soap mixture. Surgery was done almost entirely by Graefe knife section, and the wound was closed with 1 to 3 interrupted corneoscleral sutures. Instruments were placed in boiling water for a few minutes between cases.

The patients were seen postoperatively on a daily basis by the camp ophthalmologist. Atropine 1% drops and chloramphenicol 1% drops were applied at each dressing change. The patients were discharged on the seventh postoperative day with instructions to return to the area hospital for at least 1 postoperative follow-up examination. On discharge from the camp each patient was given a pair of cataract glasses equal to their retinoscopic spherical equivalent.

On this regimen the endophthalmitis rate was 3·6%. Between 1961 and 1975 a total of 50 791 cases were operated upon in the above manner, and 1825 developed bacterial endophthalmitis (Sathar, 1976). The patients with endophthalmitis were treated with intramuscular tetracycline twice daily and oral prednisolone daily. Intraocular injections of antibiotic solutions, including chloramphenicol and gentamicin, were also initiated during the past 3 years. In our study, when intracameral injection was used, 0·2 ml of a saline solution containing 50 μg of gentamicin was injected into the anterior chamber of each eye immediately after placement of the corneoscleral sutures. As in the previous eye camps, the surgeons were attending and house staff ophthalmologists from the Government Erskine Hospital, Madurai. No changes were made

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Table 1 *Incidence of endophthalmitis and other complications among the operated cases*

Camp no.	*Group*	*No. of cases*	*Anterior chamber shallow*	*Cortex retained in anterior chamber*	*Endophthalmitis*	*Hyphema*	*Iris prolapse*
1	1	219	6	11	6	2	...
2	2	369	16	4	5	3	7
3	3	146	5	8	1	3	
4	3	195	19	12	1	2	
5	3	302	6	9	2	5	
6	3	260	6	14	2	8	3
7	3	168	5	1	...	4	2
8	3	367	4	6	...	3	2
Total		2026	67	65	17	30	14

in the original procedure or in the preoperative selection and preparation of the patients or in their postoperative care. The camps in our study were sequentially divided into 3 groups:

Group 1: No prophylactic intracameral gentamicin was given. Oral and topical chloramphenicol was used for all patients as described in the original protocol.

Group 2: Prophylactic intracameral gentamicin was used for the female patients only. No chloramphenicol was used for the female patients. Oral and topical chloramphenicol was given to all male patients as described.

Group 3: Prophylactic intracameral gentamicin was used for all patients in this group. No chloramphenicol or any other antibiotic was given to any of these patients.

Results

Group 1: In camp 1 a total of 219 cataract extractions were performed. Six eyes developed postoperative endophthalmitis, an incidence of 2·9% in this camp.

Group 2: In the second camp all the female patients received intracameral gentamicin, and the male patients were treated as in Group 1. A total of 188 female patients had cataract extractions, with no cases of endophthalmitis. Five of the 181 male patients having cataract extractions developed endophthalmitis, an incidence of 2·8%.

Group 3: In camps 3 to 8 all patients received intracameral gentamicin. Among 1438 patients in this group there were 6 cases of postoperative endophthalmitis, an incidence of only 0·42%.

The combined incidence of postoperative endophthalmitis in the patients in group 3 and those treated with intraocular gentamicin in group 2 was 0·37%.

Table 1 summarises the postoperative complications in each camp including the cases of endophthalmitis. 11 cases of endophthalmitis were diagnosed in groups 2 and 3. Aspiration of 0·1 ml of vitreous was performed in each of these cases, and cultures were done using cooked meat and chocolate agar media. Each of the 11 cases was culture positive as listed in Table 2.

All the cultured organisms were sensitive to gentamicin. Each case of endophthalmitis was treated with a combination of gentamicin and dexamethasone. A total of 400 μg of gentamicin and 360 μg of dexamethasone was given by a single intravitreal injection according to our technique (May *et al.*, 1974; Peyman *et al.*, 1974a; Peyman *et al.*, 1974b). The ocular media cleared in 9 of the 11 cases after this single treatment. The other 2 eyes did not clear completely, and eventually progressed to phthisis bulbi.

Discussion

The rate of endophthalmitis in the South Indian eye camps has been 3·6% over the past 14 years. This is comparable to the 2·9% incidence of endophthalmitis in those patients in our series not treated with intracameral gentamicin. This high incidence is attributable to the inability to achieve asepsis in the temporary operating rooms prepared in the village eye camps. Even with the best of efforts flies are present and sterile technique cannot be achieved.

Of 1626 patients receiving prophylactic intraocular gentamicin at operation only 6 developed bacterial endophthalmitis, an incidence of 0·37%. This study shows that a substantial decrease in the incidence of endophthalmitis has been achieved with

Table 2 *Results of vitreous aspirate culture*

Organism cultured	*No. of cases*
Staphylococcus albus	3
Coliform and *S. aureus*	1
S. aureus	2
Beta-haemolytic streptococcus	1
S. pyogenes	1
Pseudomonas aeruginosa	3
Total	11

this method. We believe that the routine intraocular injection of small quantities of gentamicin, i.e., 50 μg, could greatly reduce the incidence of postoperative endophthalmitis in many parts of the world where surgical asepsis is a problem.

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Microfilaria malayi in uveitis: Case report

K. ANANDAKANNAN AND C. P. GUPTA

SUMMARY A case of uveitis with microfilariae in the anterior chamber is reported. The organism was recovered from the aqueous and identified as *Brugia malayi*

The first recorded case of an intraocular filaria was published by Mercier (1771), and numerous cases have since been reported. Here we present a case of unilateral uveitis with the presence of microfilaria in the anterior chamber confirmed by aqueous puncture and microscopy as *Brugia malayi*.

Case history

The patient, a man aged 60 years, came from a place endemic for filariasis and reported to the Government Ophthalmic Hospital on 14 July 1976 complaining of redness and watering in the right eye of 1 week's duration. It was acute in onset and he had had no previous attacks. There was no history of having had fever with rigor suggestive of filariasis.

On general examination there was no lymphadenopathy; the inguinal group of glands especially were normal. There was a minimal hydrocoele of the scrotum on both sides. Examination of the right eye showed swelling of the lid and ciliary injection. The cornea was clear. The pupil was small and reacted sluggishly to light. A posterior cortical cataract was present. The right vision was 6/60. The fundus view was hazy but the disc appeared normal. Slit-lamp examination showed no KPs but a marked aqueous flare and many cells in the anterior chamber.

Subsequent slit-lamp examination done a week after admission showed the presence of a few actively motile organisms in the anterior chamber. They were seen only in the pupillary area and appeared to be attached to the anterior lens capsule. The intensity of the flare and cells remained the same. The patient was put on routine therapy for uveitis. The aqueous was tapped and a drop examined beneath a cover slip under the microscope.

Actively motile organisms were found to be swarming in the field. Paracentesis was repeated after 3 days and the same type of organisms were found to be present in the aqueous. However, attempts to stain the organisms were unsuccessful. Photographs of the organisms could not be made owing to the poor background despite several attempts.

Investigations

Urine: albumin, sugar—nil. Mantoux test—positive. Blood VDRL—positive in 1 dilution. Total white cell count—8·2 × 10^9/l; polymorphs 50%, eosinophils 12%, lymphocytes 38%. ESR—0·5 hour 5 mm—1 hour 10 mm.

Night blood was positive for microfilaria. A smear was done and stained with iodine, which showed the presence of microfilariae. Owing to the presence of nuclei up to the tail tip and its bifurcation at the tip it was identified as the genus *Brugia malayi* (Figs. 1 and 2). The patient was started on diethylcarbamazine systemically 2 mg/kg body weight for 15 days. Locally he had atropine and cortisone applied thrice daily. The eye became quiet in 1 week and slit-lamp examination done after 2 weeks showed no flare or cells; a few microfilariae were still seen in the anterior chamber, but they were fewer in number and less motile. Subsequently, the patient was discharged and advised to come after a month for follow-up.

Discussion

The filariae are parasites belonging to the group of nematodes. Four types are pathogenic to man; *Wuchereria bancrofti*, causing filariasis; *Onchocerca volvulus*, causing onchocerciasis; *Loa loa*, causing loaiasis; and *Dracunculus medinensia*, causing dracunculiasis. Filariasis is transmitted by a mosquito which harbours the larvae and microfilariae. Five types of microfilaria are found in blood. *Mf. bancrofti*, *Mf. malayi*, and *Mf. loa*, which are sheathed and have a periodicity. *Mf. perstans* and *Mf. ozzardi* are non-sheathed and non-periodic. *Mf. bancrofti* and *malayi* are common in India.

Brugia malayi can occur alone or in conjunction

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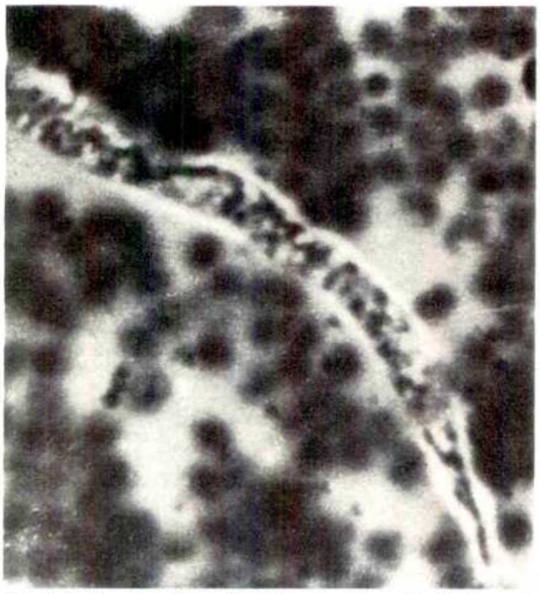

Fig. 1 *Showing the tail of the parasite with birfurcated nucleus*

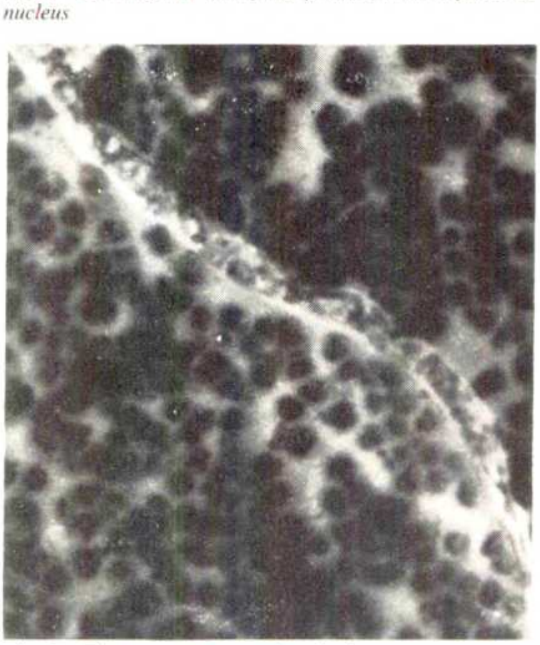

Fig. 2 *The parasite seen under the low power microscope*

with bancroftian filaria. The adult worm is found in the lymphatic system; microfilariae are found in the peripheral blood at night. They show the following peculiarities: (1) Small in size (230 × 6 μm); (2) secondary kinks instead of smooth curves; (3) double stylets at anterior end; (4) cephalic space broad; (5) tail tip not free from nuclei.

The intermediate hosts are various species of *Mansonioides* and certain species of *Anopheles* mosquito. Domestic animals, cats, and dogs may serve as reservoirs of infection (Chatterjee, 1971).

The ocular manifestations of filariasis are elephantiasis of the eyelids; iritis caused by the adult worm; retinal haemorrhages or the presence of microfilariae in the lachrymal gland secretion (Toussaint and Davis, 1965). The microfilariae liberated from the adult worm inhabiting the lymphatics of the pelvis and lower part of the abdomen enter the venous system through the thoracic duct (Jones *et al.*, 1938). After going through the pulmonary circulation they enter the systemic circulation. Entry into the anterior chamber may be through the ciliary vessels.

The presence of an adult worm in the anterior chamber producing iritis has been reported by many authors (Nayar and Pillai, 1932; Wright, 1934). Sun (1958) in China observed microfilariae swimming actively in the anterior chamber. With diethylcarbarmazine and carbosone the microfilariae disappeared from the blood in 1 month and from the anterior chamber in 4 months (Duke-Elder, 1965). Probably this is the first report from India in which microfilariae have been seen and isolated from the anterior chamber.

Living microfilariae in the blood do not produce any pathogenic effect. But in this case, as the routine investigations were negative and the uveitis responded to diethylcarbamazine it may be a rare case of uveitis caused by the microfilariae in the anterior chamber.

We hereby acknowledge our thanks to the Superintendent, Government Ophthalmic Hospital, Madras, for having permitted us to publish this article. We also thank Dr Subramanian, Professor of Bacteriology, Madras Medical College, who helped in identifying the microfilariae.

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Uveal involvement in Marburg virus disease

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SUMMARY The first reported case of uveal involvement in Marburg virus disease is described. '*Ex Africa semper aliquid novi*'.

Two outbreaks of Marburg virus disease have been documented. The first occurred in Marburg and Frankfurt, West Germany, in 1967 (Martini, 1969) and the second in Johannesburg in 1975 (Gear, 1975). This case report describes the third patient in the Johannesburg outbreak, who developed an anterior uveitis. The cause of the uveitis was proved to be the Marburg virus by identiying it in a tissue culture of her aqueous fluid.

Case report

Before describing the case history of the patient the events leading to her contracting the disease must be briefly described. The full details of the 3 patients affected have already been reported (Gear, 1975).

A 20-year-old Australian man was admitted to hospital on 15 February 1975. He had just returned from Rhodesia when he developed myalgia, vomiting, high fever, and a mild lymphadenopathy. He also had intensely congested conjunctivae. There was a recent insect bite in the right flank. He had a pronounced leucopaenia but peripheral smears for malaria and trypanosomiasis were negative. He was diagnosed as suffering from typhoid fever and treated accordingly. He developed profuse blood-stained diarrhoea and vomiting and his renal function deteriorated rapidly. There was a maculopapular rash. Peripheral blood smears suggested a viral infection. Examination of his stools was negative for plague. Despite the most intensive therapy he died from hepatorenal failure 4 days after admission. He had a terminal disseminated intravascular coagulopathy.

Two days after his death his 20-year-old girl friend presented with similar initial complaints. She had accompanied him on his travels through Rhodesia and had also been constantly at his bedside till his death. Lassa fever was suspected and she was given a unit of Lassa fever convalescent serum when she became desperately ill on the fifth day. She also developed acute pancreatitis. Within 52 hours she made a dramatic and uneventful recovery. Her illness mainly affected the haematopoietic, hepatic, and pancreatic systems.

The subject of this report was a nurse who had helped to nurse patients 1 and 2. Nine days after the death of the first patient she presented with lower back pain and high fever. She developed hepatitis, a mild disseminated intravascular coagulation syndrome, successfully treated with heparin, and the classical rash for the disease. She also had injected conjunctivae.

She was given Lassa fever convalescent serum but did not respond within 48 hours. For the first time Marburg virus disease was suspected. On day 7 she spontaneously improved. She was discharged after 21 days, when the diagnosis of Marburg virus disease was confirmed.

Three months after her recovery she came to the eye department complaining of a painful right eye and blurred vision for the past 2 weeks. She was constitutionally well. Her visual acuity was right eye 6/7·5, left eye 6/6. The left eye was normal in all respects. The right eye showed mild congestion of the conjunctiva, a + flare and + + cells in the anterior chamber, and an intraocular pressure of 50 mmHg. The vitreous, disc, macula, and peripheral retina were all normal. The retina showed a number of small, yellowish-white drusen bodies. No vitreal reaction was seen over them and their appearance has remained unchanged since they were first observed. Fluorescein angiography was normal. Gonioscopy showed a normal angle. She was started on acetazolamide, atropine, and topical corticosteroids 2 hourly. The tension was rapidly controlled and diamox was stopped after 3 days. Subsequent daily measurements showed no increase of her

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tension. She developed white keratic precipitates in her right eye. A full uveitis battery was negative.

Seven days after her presentation her anterior chamber was still active and an aqueous tap was performed. Tissue culture of the aqueous yielded Marburg virus. Typical inclusion bodies were found in the cytoplasm of vero cells. The iritis slowly decreased and a repeat tissue culture of aqueous 2 weeks later was negative. Two months later and again in January 1976, she had further attacks of iritis. These both resolved rapidly without any untoward sequelae.

Discussion

Marburg disease is a pantropic acute febrile infection due to a highly pathogenic virus transmitted by vervet monkeys (*Cercopithecus aethiops*). It belongs to no taxonomonic group. It has an incubation period of 7 days. The differential diagnosis includes all haemorrhagic fevers such as yellow fever, plague, typhus, malaria, and Lassa fever. The clinical features of Marburg virus disease are very similar to Lassa fever, so named after the area of West Africa where it first occurred (Monath, 1974). Both diseases are characterised by high mortality and person-to-person transmission. Their importance in public health is obvious.

The diagnosis of Marburg virus disease was jointly made at the Centre for Disease Control, Atlanta, USA, and the Poliomyelitis Research Foundation, Johannesburg, South Africa. A fluorescent antibody was also shown to develop in the sera of all 3 patients against the isolated Marburg virus.

This is the first reported case of Marburg fever as a cause of uveitis. The diagnosis was proved by tissue culture of aqueous. Since this was positive while the patient had raised serum antibody levels we may assume that the antibody had not neutralised live virus in the uveal tract cells. This point was particularly important as the patient was about to start an obstetric course. Nevertheless, cultures of stool, urine, and throat swabs were negative, and when culture of aqueous from the second tap was found to be negative she was allowed to start work. Interestingly, one of the patients in the 1967 outbreak had circulating antibodies and yet transmitted the disease venereally. Live virus was isolated from his semen.

The disease was thought at first to be endemic for Uganda and Kenya, but this is obviously incorrect. It now extends down to Rhodesia and possibly the Republic of South Africa.

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The association of rubeosis iridis with endothelialisation of the anterior chamber: report of a clinical case with histopathological review of 16 additional cases

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SUMMARY A patient is reported in whom the clinical observation of extension of the corneal endothelium and Descemet's membrane in association with rubeosis iridis was confirmed by histopathological examination. In a study of eyes which had been removed and demonstrated rubeosis iridis and secondary glaucoma 16 additional eyes revealed extension of the corneal endothelium and Descemet's membrane on to the anterior iris surface. In all instances the transition occurred at the pseudoangle formed by the attachment of peripheral anterior synechiae. The suggestion is made that the fibrovascular membrane of rubeosis iridis is the stimulus which excites the extension of the endothelium on to the iris surface. The association between rubeosis iridis and extension of the corneal endothelium and Descemet's membrane on to the iris has not been previously appreciated.

The extension of corneal endothelium and Descemet's membrane on to the anterior iris surface has been reported: (1) in the presence of peripheral anterior synechiae; (2) in association with the iris-naevus syndrome; (3) on the trabecular meshwork following traumatic angle recession; and (4) in essential iris atrophy. When examining a patient's blind eye prior to enucleation we observed a glass-like membrane on the anterior surface of the iris in association with ectropion uveae, peripheral anterior synechiae, and rubeosis iridis. Histopathological confirmation of the clinical findings led us to undertake a retrospective study of enucleated eyes displaying rubeosis iridis and peripheral anterior synechiae which also showed extension of corneal endothelium and Descemet's membrane on to the anterior iris surface.

Case report

A 50-year-old man was examined in September 1975 because of an irritated, blind right eye. He had been struck by a snowball at age 11 and had subsequently undergone a slow, progressive loss of vision. The patient had been in excellent health all his life. On examination in 1975 his corrected visual acuity was no light perception right eye and 20/20 left eye. Intraocular pressure was 16 mmHg OD and 18 mmHg OS, by applanation. The left eye was entirely normal, while examination of the right eye revealed a moderately hyperaemic conjunctiva, clear cornea, and an anterior chamber much deeper than on the right associated with a posteriorly dislocated, cataractous and partially calcified lens. The anterior chamber angle was closed for 360° by broad peripheral anterior synechiae. The iris displayed 360° of extensive ectropion uveae with the iris pigment epithelium reflected nearly 50% on to the anterior iris surface (Fig. 1). Where the ectropion ceased, a prominent rubeosis iridis was apparent. Overlying the rubeosis iridis a glass-like, gossamer membrane was present on the anterior iris surface extending

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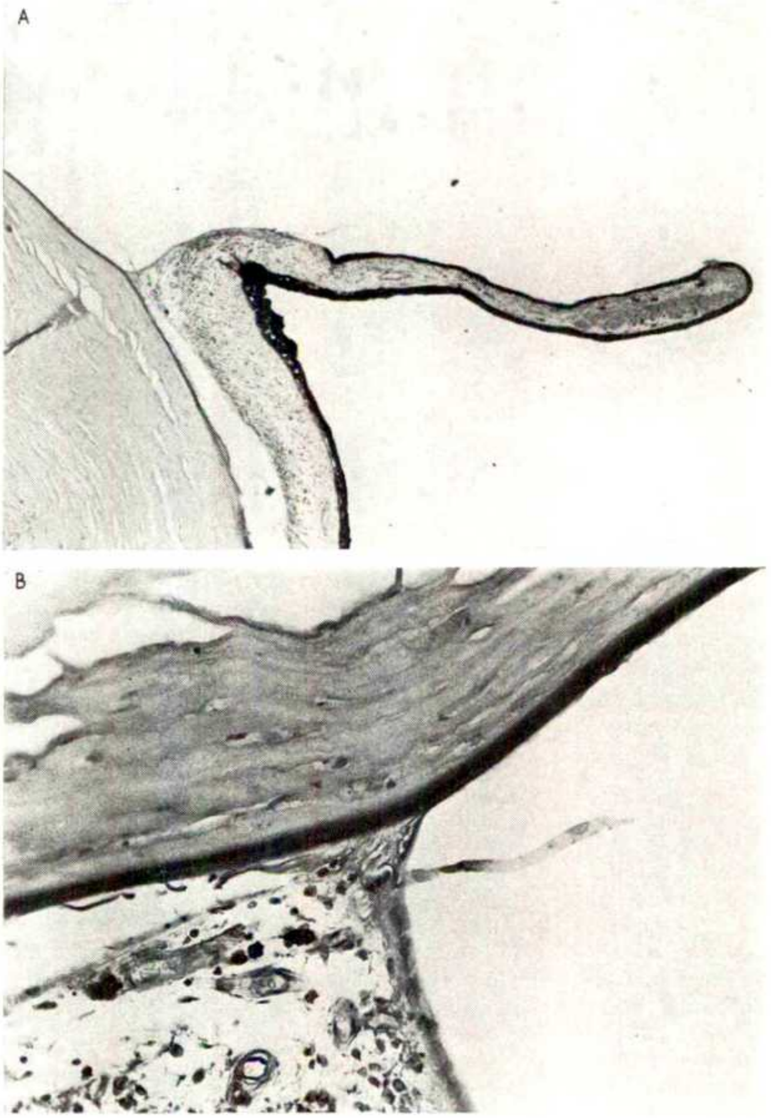

Fig. 1 A. *Photomicrograph revealing extensive ectropion uveae with rubeosis iridis. H and E.* ×50. B. *Higher power view of angle showing extension of endothelium and Descemet's membrane on to iris. PAS.* ×315

from the pseudoangle formed at the termination of the peripheral anterior synechiae to the border of the ectropion uvea. The retina was totally detached as delineated by contact B-scan ultrasonography. The eye was enucleated.

Histopathological study

GROSS EXAMINATION

The specimen consisted of an intact right eye measuring 26 × 26 × 24 mm. The cornea measured 12·5 × 11·5 mm and was clear. The pupil measured 4 mm in diameter and the iris showed a marked ectropion uveae. The eye was opened horizontally and the retina displayed a total detachment with a large amount of crystalline material in the subretinal space. A dislocated, cataractous lens was present inferiorly.

MICROSCOPIC EXAMINATION

The subconjunctival tissue showed a moderate round cell infiltration. The cornea was unremarkable, and the anterior chamber angle on both sides showed evidence of a previous angle recession with secondary peripheral anterior synechiae. At the site of the recession there was some fibrosis. The iris was markedly thinned and showed a very prominent ectropion uveae. A fibrovascular membrane was present on the iris surface extending from the peripheral anterior synechiae to the ectropion uveae. At the pseudoangle there was extension of Descemet's membrane and endothelium on to the anterior surface of the iris (Fig. 1). The dislocated lens was calcified and the totally detached retina was atrophic.

Impression

(1) Anterior chamber angle recession.
(2) Peripheral anterior synechiae.
(3) Rubeosis iridis.
(4) Ectropion uveae.
(5) Extension of endothelium and Descemet's membrane on to the anterior surface of the iris.
(6) Total retinal detachment.
(7) Cataract with calcification.

Case material

The findings in our case prompted us to undertake a retrospective study of enucleated eyes. In our histopathological collection of eyes with rubeosis iridis we found 16 globes which also had an extension of the corneal endothelium and Descemet's membrane on to the iris. The results in these cases are summarised in Table 1. Of the 16 eyes displaying an extension of Descemet's membrane on to the iris 14 eyes were surgical enucleations and 2 were postmortem specimens. Seven of the eyes had severe trauma, 3 eyes had previous cataract extractions, 2 followed central artery occlusion, and 1 patient with diabetes mellitus had had radiation therapy (Table 2).

The corneal endothelium and Descemet's membrane grew from the cornea on to the anterior iris surface at the pseudoangle formed by the attachment of the iris to the cornea and then extended for a variable distance on to the anterior surface of the iris. This membrane was firmly attached to the iris by the fibrovascular membrane typical of rubeosis iridis. Many of the globes had ectropion uveae and pupillary membranes as well. The layer of newformed Descemet's membrane was thick and prominent and extended over most of the iris in 6 patients (Fig. 2). In 10 cases the membranes were

Table 1 *Summary of cases*

Case	*Age*	*Sex*	*Antecedent history*	*Clinical eye diagnosis*	*Peripheral anterior synechiae*	*Rubeosis iridis*
1	68	F	Extra-capsular Cataract extraction Cardiac failure	Glaucoma, Bullous keratopathy	Present	Present
2	73	M	Intra-capsular Cataract extraction Diabetes mellitus	Glaucoma	Present	Present
3	22	F	Intraocular foreign body 12 years ago. Retinal detachment operation	Blind painful eye	Present	Present
4	21	M	Blunt injury 13 years ago	Glaucoma. Rubeosis iridis	Present	Present
5	64	M	Blunt injury 46 years ago	Absolute glaucoma	Present	Present
6	52	F	Blunt injury ? date	Glaucoma. Rubeosis iridis, cataract	Present	Present
7	58	M	Blunt injury ? date	Painless blind eye	Present	Present
8	48	F	Blunt trauma 2½ years ago	Absolute glaucoma	Present	Present
9	14	F	Trauma—age 3	Glaucoma	Present	Present
10	?	?	Trauma	Sympathetic ophthalmia	Present	Present
11	?	F	Central retinal artery occlusion	Absolute glaucoma	Present	Present
12	89	F	Central retinal artery occlusion	Absolute glaucoma	Present	Present
13	54	F	Diabetes. Radiation therapy for Rubeosis iridis	Absolute glaucoma	Present	Present
14	42	M	Bilateral Peters's Anomaly	Peters's anomaly	Present	Present
15	57	F	?	Phthisis bulbi	Present	Present
16	?	F	?	?	Present	Present

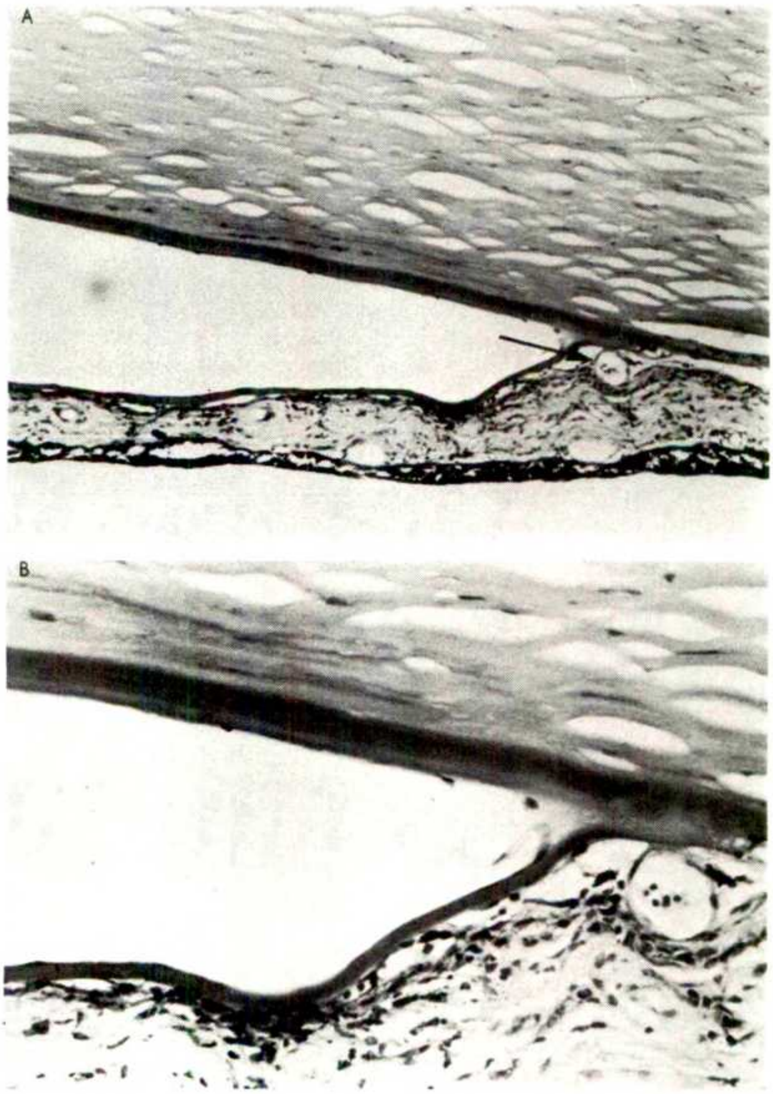

Fig 2 A. *Photomicrograph of case 7 showing prominent rubeosis iridis in presence of extension of endothelium and Descemet's membrane on to anterior iris surface. PAS.* ×135. B. *Higher power view showing prominent vessels between new-formed Descemet's membrane and anterior iris surface. PAS.* ×800

Table 2 *Distribution of cases of endothelialisation of the anterior chamber*

Category	*Number of cases*
1. Trauma A. Surgical	2
B. Non-surgical	9
2. Central retinal artery occlusion	2
3. Diabetes mellitus	1
4. Peters's anomaly	1
5. Unknown	2
	17

thin and partial and extended only a short distance from the pseudoangle.

Discussion

Corneal endothelium and Descemet's membrane may under certain circumstances extend from their normal position on the cornea: (1) over the trabecular meshwork following anterior chamber angle recession (Wolff and Zimmerman, 1962); (2) over the iris in association with the iris naevus syndrome (Klien, 1941; Cogan and Reese, 1969; Wolter and Makley, 1972; Scheie and Yanoff, 1974); (3) over the anterior iris surface in association with peripheral anterior synechiae (Wagenmann, 1889); and (4) in essential iris atrophy (Heath, 1953).

Collins (1927) reported a case of buphthalmos where failure in the normal development of the anterior chamber angle was associated with a continuation of Descemet's membrane at the angle on to the surface of the iris. Reese (1944) noted the presence of Descemet's membrane on the trabecular area in association with open-angle glaucoma. Lauring (1969) reported 19 cases of Descemet's membrane extending on to the iris. In 13, peripheral anterior synechiae were present while in 6, which occurred after trauma, Descemet's membrane and endothelium extended over the recessed angle. Wolff and Zimmerman (1962) in their study of traumatic recession of the angle described Descemet's membrane extending over the inner surface of the trabecular meshwork and the recessed angle or extending from the pseudoangle formed at the attachment of peripheral anterior synechiae. Klien (1941) reported a patient, and Cogan and Reese (1969) added 2 additional cases in which superficial iris nodules were associated with peripheral anterior synechiae and extension of corneal endothelium and Descemet's membrane on to the iris surface. The nodules on histopathological examination were naevi and they called the condition the iris-naevus syndrome. Wolter and Makley (1972) reported a similar case. Scheie and Yanoff (1975) reported 14 such patients, all of whom had glaucoma, peripheral anterior synechiae, and iris nodules. Many had ectropion uveae. In 3 of their cases histopathological examination revealed extension of the corneal endothelium and Descemet's membrane on to the anterior iris surface. Additionally, late failure of filtering surgery for glaucoma in association with the iris naevus syndrome may be due to endothelialisation of the filtering bleb associated with the production of a thick basement membrane (Yanoff *et al.*, 1976).

Waring *et al.* (1974) in a review of the laterature of pathological alteration of Descemet's membrane found no adequate explanation for the normal limitation of the endothelium and Descemet's membrane to the cornea nor for its extension on to the iris. Review of the literature reveals 2 modes of extension of Descemet's membrane. In 1 type Descemet's membrane grows over the trabecular meshwork of an open or recessed angle. Most of these cases followed trauma associated with angle recession. The other type is an extension of Descemet's membrane from the cornea at the pseudoangle formed by peripheral anterior synechiae on to the iris surface. Most of the cases in the literature as well as our 17 cases are of the second type. Since all of our cases reported here were in association with rubeosis iridis this number suggests that rubeosis iridis may be a factor in the extension of endothelium and Descemet's membrane on to the iris.

The accepted explanation for the development of ectropion uveae is that contraction of the fibrovascular membrane of rubeosis iridis pulls the iris pigment epithelium from the pupillary border on to the anterior iris surface. Although a definitive explanation for the extension of endothelium and Descemet's membrane on to the iris has not been set forth, it seems likely that the presence of the neovascular membrane attached to the cornea at the pseudoangle can in some way stimulate the extension of the endothelium on to the anterior iris surface. Though there are many conditions that are associated with the development of rubeosis iridis, the end result of corneal endothelium and Descemet's membrane extending on to the iris is very similar regardless of the cause of the rubeosis iridis. We found essentially identical findings in cases which followed or were in association with trauma, surgery, diabetes mellitus, Peters's anomaly, and closure of the central retinal artery.

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Behaviour of the iris vasculature in central retinal vein occlusion: a fluorescein angiographic study of the vascular response of the retina and the iris

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SUMMARY The findings in iris fluorescein angiograms of 48 eyes with central retinal vein occlusion (CRVO) were correlated with the predominant retinal vascular response. In 24 eyes with the non-ischaemic type of CRVO there were no or only minimal iris vessel changes, whereas in all 24 eyes with ischaemic type of CRVO there was iris vessel dilatation and leakage with or without neovascularisation. These findings support the hypothesis that hypoxic retina may be a cause of rubeosis iridis in CRVO.

The purpose of this study was to see whether there is any correlation between the behaviour of the iris vessels and the type of central retinal vein occlusion (CRVO). Iris neovascularisation after CRVO was described by Coats (1906). Fluorescein angiography of the iris has shown dilatation of the radial vessels and abnormal leakage of the dye in some cases of CRVO (Raitta, 1968; Raitta and Vannas, 1969; Cappin and Whitelocke, 1974; Kottow, 1976). In our study we have correlated the angiographic findings in the iris with the predominant retinal capillary response to CRVO—that is to say, either dilatation or closure—as shown by fluorescein angiography.

Patients and methods

Forty-eight patients with a recent CRVO and suitable for both fundus and iris fluorescein angiography were studied at the Retinal Diagnostic Department of Moorfields Eye Hospital in 1975. Either a slit lamp or fundus camera and 5 ml of 20% sodium fluorescein were used for angiography. Iris and fundus angiograms were taken on separate visits.

Iris angiographies were performed 1 to 52 weeks (average 13 weeks) after the onset of symptoms. In each iris angiogram the presence and source of fluorescein leakage as well as the presence of neovascularisation and ischaemic areas were recorded.

Results

The eyes were separated into two groups according to the predominant features in the retina: (1) a non-ischaemic group, characterised by dilated and leaking retinal vessels (Fig. 1 A, B); and (2) an ischaemic group with extensive capillary closure (Fig. 1 C). There were 24 eyes in each group.

The main iris changes in the non-ischaemic and ischaemic group of CRVO are shown in Fig. 2 and the Table, which also shows the mean intraocular pressure (IOP) and the mean time after the onset of symptoms when iris angiography was performed in each group.

NON-ISCHAEMIC GROUP

Fifteen of the 24 eyes showed normal iris vasculature without any leakage of the dye (Fig. 3 A, B). The mean IOP at the time of angiography was 15 mmHg (range 9 to 25 mmHg). Angiography was performed at 1 to 36 weeks (mean 13 weeks) after the onset of symptoms.

In eight eyes localised vessel dilatation and leakage were found, mainly around the pupil, but radial vessels in general did not leak and no new formed vessels were recognised (Fig. 4 A, B). The mean IOP was 16 mmHg (range 14 to 19 mmHg) and the time of study varied from 1 to 24 weeks (mean 12 weeks) after the first symptoms.

In one eye minute new vessels with mild leakage were present on the iris. The IOP was 15 mmHg and angiography was done 11 weeks after the first symptoms.

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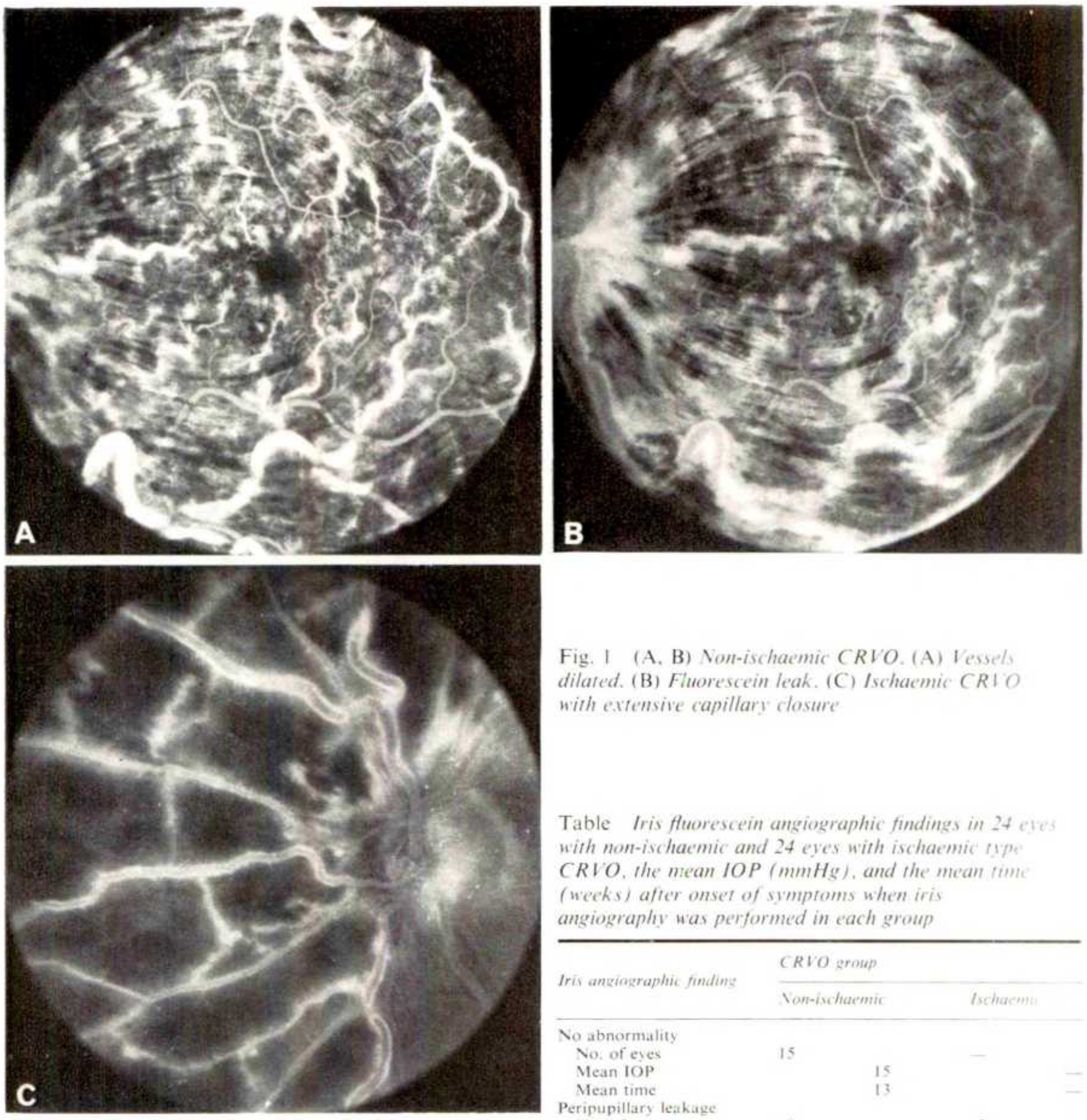

Fig. 1 (A, B) *Non-ischaemic CRVO.* (A) *Vessels dilated.* (B) *Fluorescein leak.* (C) *Ischaemic CRVO with extensive capillary closure*

Table *Iris fluorescein angiographic findings in 24 eyes with non-ischaemic and 24 eyes with ischaemic type CRVO, the mean IOP (mmHg), and the mean time (weeks) after onset of symptoms when iris angiography was performed in each group*

Iris angiographic finding	*CRVO group*			
	Non-ischaemic		*Ischaemic*	
No abnormality				
No. of eyes	15		—	
Mean IOP		15		—
Mean time		13		—
Peripupillary leakage				
No. of eyes	8		2	
Mean IOP		16		15
Mean time		12		9
Radial vessel dilatation and leakage				
No. of eyes	—		8	
Mean IOP		—		26
Mean time		—		9
Minimal neovascularisation				
No. of eyes	1		6	
Mean IOP		15		17
Mean time		11		21
Extensive neovascularisation				
No. of eyes	—		8	
Mean IOP		—		42
Mean time		—		16
Total No. of eyes	24		24	

ISCHAEMIC GROUP

All the 24 eyes showed abnormal leakage of dye from the iris vessels. In two eyes vessel dilatation and leakage were restricted to the peripupillary zone corresponding to the findings in the non-ischaemic group. The IOP was 15 mmHg in both and the study was performed nine and eight weeks after the onset of symptoms.

In six eyes small new vessels were seen on the iris with mild leakage (Fig. 5 A, B). The IOP varied from 13 to 22 mmHg (mean 17 mmHg) and the study was performed 9 to 52 weeks (mean 21 weeks)

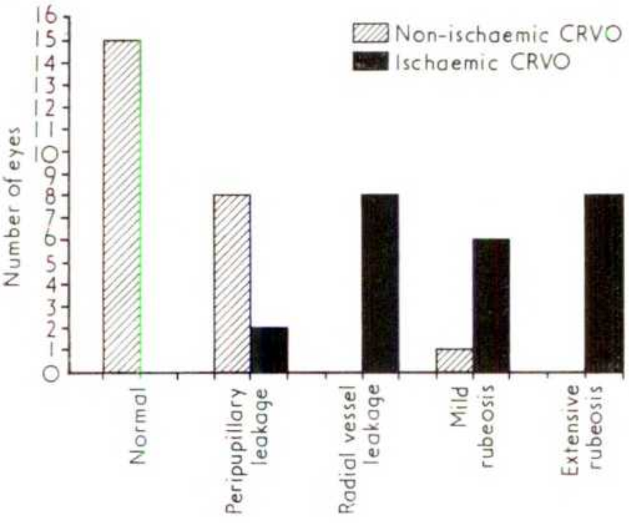

Fig. 2 *Distribution of eyes with non-ischaemic and ischaemic CRVO according to predominant findings in iris angiograms*

after the first symptoms. In most of these eyes the radial vessels were not dilated and did not leak fluorescein.

In eight eyes with ischaemic CRVO the main finding was dilatation of the radial iris vessels with moderate (four eyes) or extensive (four eyes) leakage of fluorescein, but no obvious neovascularisation could be seen in the first angiogram (Fig. 6 A, B). In these cases the angiograms were taken 1 to 19 weeks (mean eight weeks) after the first symptoms. The IOP varied from 14 to 40 mmHg (mean 26 mmHg). In one eye some ischaemic areas were seen in the iris. Six of these eyes developed rubeosis later, during follow-up (Fig. 6 C, D), and in five eyes neovascular glaucoma has appeared.

In eight eyes considerable rubeosis with leakage was already seen in the initial angiogram (Fig. 7 A, B). In every eye neovascularisation was found both around the pupil and in the periphery of the iris. In three eyes the radial vessels leaked fluorescein as well. All but one eye had already developed neovascular glaucoma. Therefore the mean IOP in this group was 42 mmHg (range 15 to 63 mmHg). The time of iris angiography varied from 4 to 36 weeks (mean 16 weeks) after the first symptoms. Two eyes showed areas of iris vessel closure.

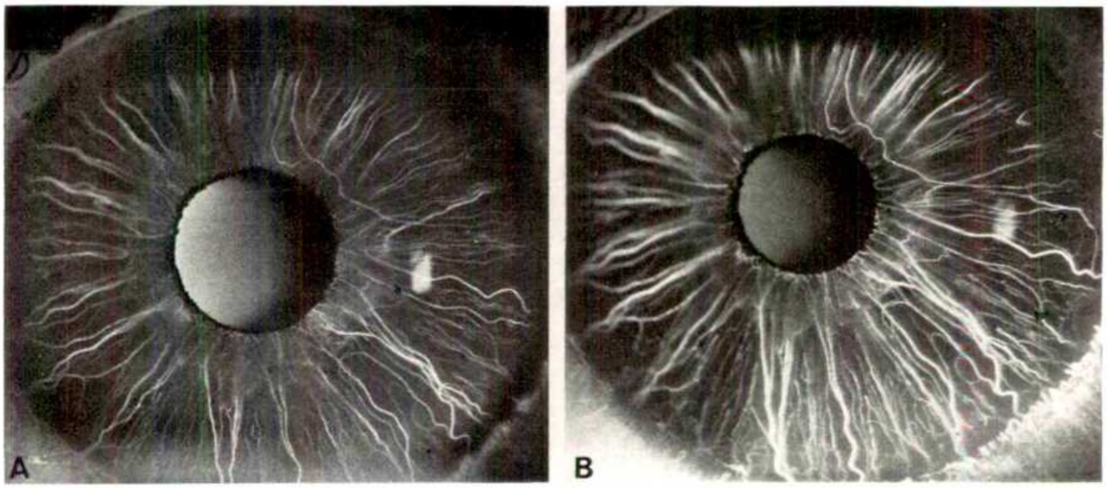

Fig. 3 *Iris angiogram in non-ischaemic CRVO.* (A) *Normal iris vasculature in arteriovenous phase.* (B) *No fluorescein leakage in late venous phase*

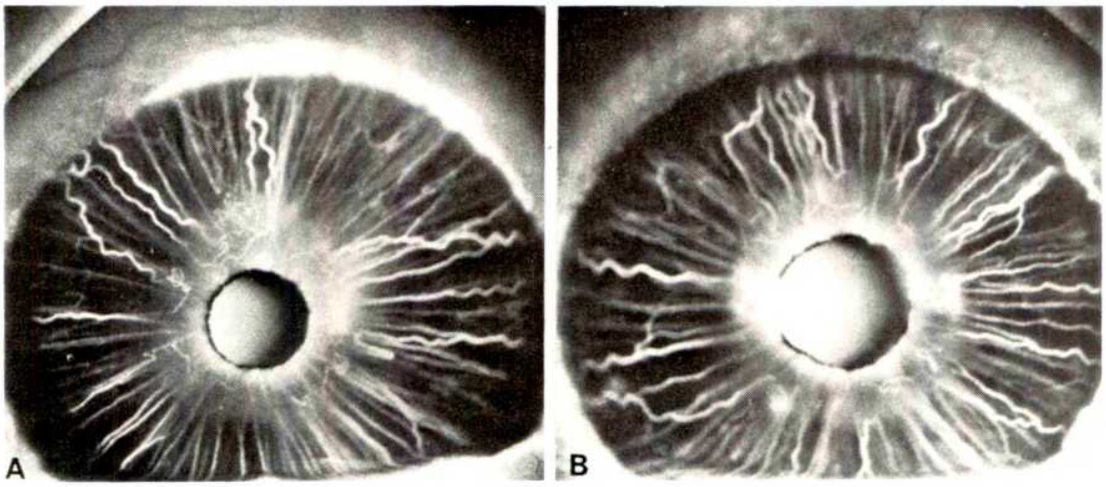

Fig. 4 *Iris angiogram in non-ischaemic CRVO.* (A) *Dilated vessel loops, and* (B) *leakage around the pupil*

Discussion

Iris fluorescein angiography permits visualisation of the radial arteries and veins as well as larger capillaries. In healthy eyes fluorescein leakage from iris vessels seldom occurs (Vannas, 1969). We found in this study that in most eyes with the non-ischaemic type of CRVO the iris vasculature was normal, although in a few cases mild vessel dilatation and leakage were seen at the pupillary margin. This result could be expected from our previous finding that neovascular glaucoma did not develop in eyes with good retinal capillary perfusion (Laatikainen and Kohner, 1976).

In contrast, in eyes with the ischaemic type of CRVO rubeosis iridis and neovascular glaucoma are common. In this type, even without glaucoma, angiographic changes of the iris were the rule. The importance of retinal non-perfusion in the development of iris neovascularisation is also supported by Kottow's report (1976), according to which iris vascular alterations were commoner in eyes with fundus neovascularisation than in those without. Fundus neovascularisation after retinal venous occlusion is also related to retinal non-perfusion.

We were unable to take iris angiograms immediately and repeatedly after the onset of the disease. Therefore the exact time of the appearance of the various iris changes could not be accurately known. Dilatation and leakage of the radial vessels seemed,

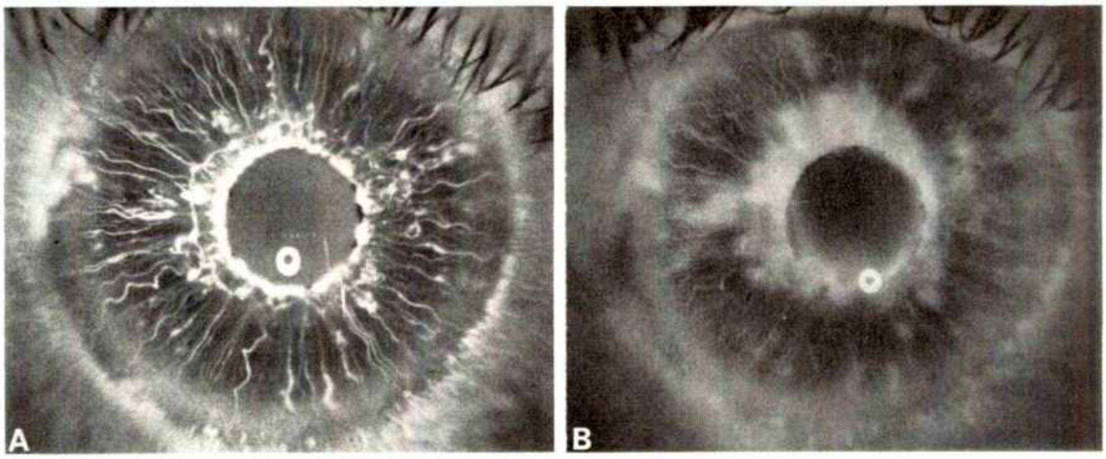

Fig. 5 *Iris angiogram in ischaemic CRVO.* (A) *Small new vessel tufts which* (B) *leak fluorescein*

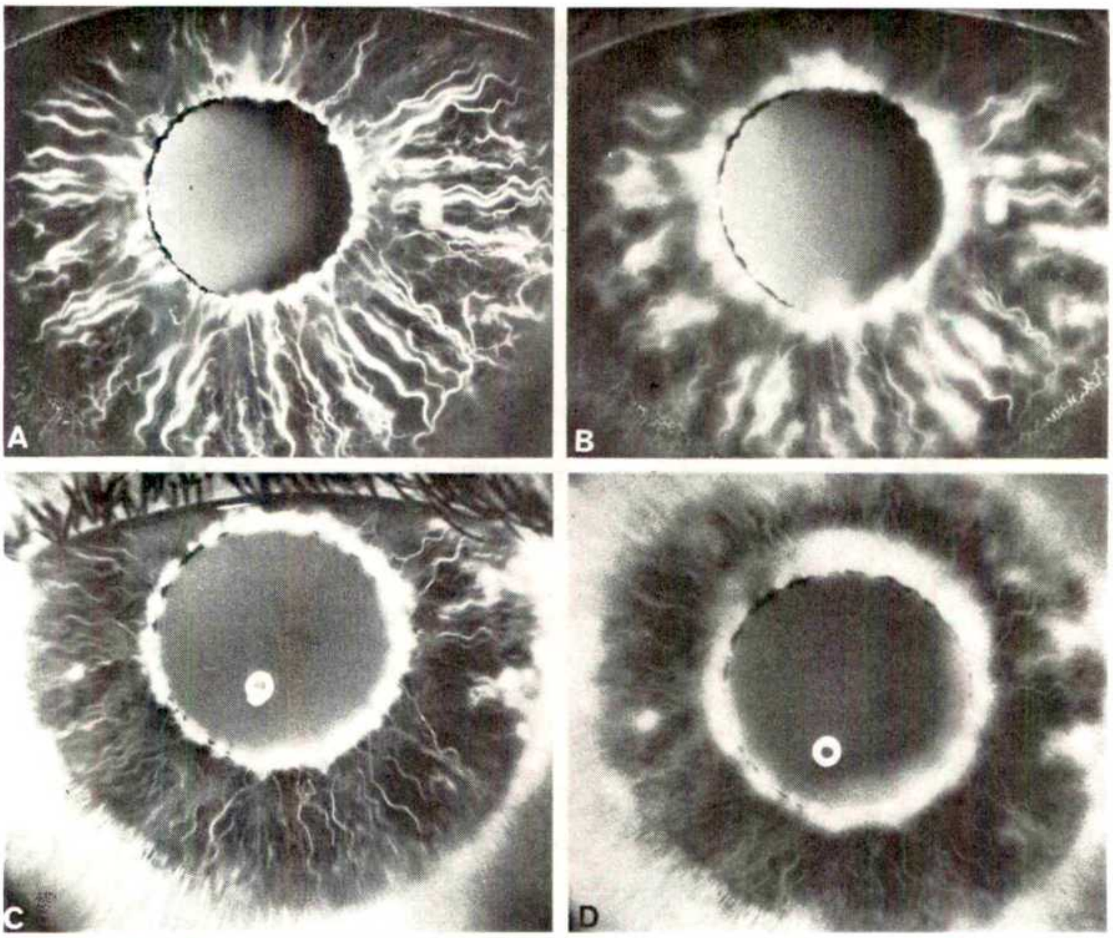

Fig. 6 (A, B) *Iris fluorescein angiogram three months after initial symptoms in ischaemic CRVO.* (A) *Radial vessels dilated and* (B) *leak fluorescein.* (C, D) *Same iris eight months later.* (C) *Central and peripheral neovascularisation with* (D) *leakage only from new vessels*

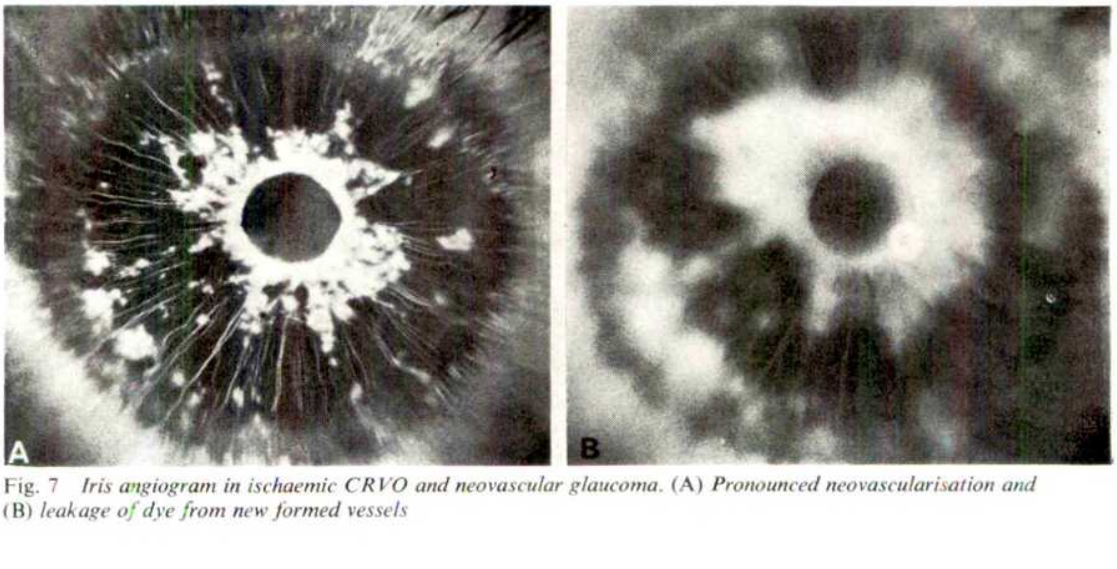

Fig. 7 *Iris angiogram in ischaemic CRVO and neovascular glaucoma.* (A) *Pronounced neovascularisation and* (B) *leakage of dye from new formed vessels*

however, to precede iris neovascularisation. Similar changes were also described by Vannas and Raitta (1972) in two eyes with CRVO. Later in most early rubeotic eyes radial vessels looked quite normal. Permanent closure of the iris vessels was found only in eyes with a high IOP due to neovascular glaucoma, and therefore vascular closure was possibly secondary to glaucoma. This agrees with the findings of Cappin and Whitelocke (1974), who could not find any signs of defective iris perfusion in early rubeotic eyes.

Iris neovascularisation has been experimentally produced by occluding the long ciliary arteries (Anderson and Morin, 1971). But local vascular insufficiency of the iris would seem unlikely to be the primary cause of rubeosis iridis in CRVO, although the possibility of a transient ischaemia and vessel damage in the iris during the acute stage of the disease could not be excluded. In our cases iris changes closely correlated to the type of the predominant retinal response to CRVO. Destroying the hypoxic retina by photocoagulation also seems to arrest rubeosis (Laatikainen, 1977). These findings support the hypothesis that iris neovascularisation is stimulated by some factor diffusing from the hypoxic retina (Ashton, 1961). The first appearance of neovascularisation around the pupil and in the angle, in the position of maximum turnover of contact with aqueous humour, was also considered by Smith (1961) as an indication of the presence of some vasoformative factor, presumably a product of the hypoxic retina, in the anterior chamber fluid.

Post-thrombotic hypotony has also been suggested as a cause of iris changes. Cappin and Whitelocke (1974) described leakage from radial iris vessels in hypotonic eyes only with tensions of less than 10 mmHg. None of the eyes with leaking radial vessels among our cases was hypotonic. This indicates that low IOP was unnecessary for radial vessel leakage or developing rubeosis, and agrees with the findings of Vannas and Raitta (1970) that the incidence of haemorrhagic glaucoma was not increased by post-thrombotic hypotony.

We thank Dr Eva Kohner, who looked after the medical side of these patients, and Mr K. Sehmi for his assistance with the photographs.

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Preliminary report on effect of retinal panphotocoagulation on rubeosis iridis and neovascular glaucoma

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SUMMARY Eight eyes with central retinal vein occlusion one eye with old central retinal artery occlusion complicated by rubeosis iridis or increased intraocular pressure, or both; and one eye with diabetic retinopathy and rubeosis iridis were treated by retinal panphotocoagulation. Vision did not improve but intraocular pressure was lower and iris neovascularisation regressed in most cases, supporting the hypothesis that retinal hypoxia is a cause of iris neovascularisation and suggesting that retinal panphotocoagulation has a potential prophylactic and therapeutic role in rubeosis iridis and early neovascular glaucoma.

Central retinal vein occlusion (CRVO) with capillary non-perfusion predisposes to retinal neovascularisation and rubeosis iridis (Laatikainen and Kohner, 1976). Studies on diabetic retinopathy suggest that destroying large areas of hypoxic retina or reducing its metabolic demands prevents neovascularisation and may cause retinal vessels to regress (Taylor, 1970). It was therefore decided to try this therapy in cases of retinal capillary non-perfusion and iris neovascularisation to see whether it would prevent neovascularisation or make it regress.

Rubeosis iridis may be associated with various eye diseases (Schulze, 1967), but the two most important causes of iris neovascularisation are diabetes and CRVO. In many cases rubeosis results in peripheral anterior synechiae and thrombotic or neovascular glaucoma. A follow-up study on CRVO showed that neovascular glaucoma appeared only in eyes with extensive retinal capillary non-perfusion, and in these eyes it was a common complication (Laatikainen and Kohner, 1976).

There is no known prophylactic treatment for rubeosis iridis, and neovascular glaucoma is often very resistant to any form of therapy. Obliteration of optic disc neovascularisation may occur after extensive photocoagulation of the hypoxic retina both in diabetes (Taylor, 1970) and after retinal branch vein occlusion (Kohner and Shilling, 1976). This paper is a preliminary report of the effect of retinal panphotocoagulation on rubeosis iridis and neovascular glaucoma.

Material

The material comprised 10 eyes. Eight of them had a recent CRVO. Of these eight, six had neovascular glaucoma, one had normal intraocular pressure in spite of rubeosis iridis, and one had raised intraocular pressure due to acute angle closure although there was no rubeosis. The ninth eye had neovascular glaucoma due to an old central retinal artery occlusion (CRAO) (or ischaemic type of CRVO) and the tenth eye had diabetic retinopathy and rubeosis iridis. Further clinical data on the 10 cases are summarised in the Table.

All eyes were treated by panretinal xenon arc photocoagulation avoiding the macular area. In most cases more than 400 burns of 4·5° spot size were applied. All patients received a thorough ophthalmic examination, including fundus photography and fluorescein angiography as well as iris fluorescein angiography, both preoperatively and after treatment. A routine angiographic technique with either a fundus or slit-lamp camera and 5 ml of 10 to 20% sodium fluorescein was used. The patients have been followed up for 6 to 19 months (mean 11 months) after photocoagulation.

Results

All eyes with CRVO had an ischaemic type of retinal response with extensive capillary closure

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Table *Clinical data in 10 cases of neovascular glaucoma and/or rubeosis iridis before and after retinal panphotocoagulation*

Case No.	*Preceding eye disease*	*Pretreatment*					*Time of treatment after first symptoms (months)*	*Follow-up after treatment (months)*	*Posttreatment (latest)*					
		Visual acuity	*IOP (mmHg)*	*Rubeosis iridis*	*Chamber angle*	*Pain in eye*			*Visual acuity*	*IOP (mmHg)*	*Rubeosis iridis*	*Chamber angle*	*Pain in eye*	*Other treatment*
1	CRVO	HM	56	– –	Open, NV	No	2	11	HM	25	–	⅗ closed	No	—
2	CRVO	HM	63	– –	Closed	Mild	3	19	NPL	18	+	⅓ closed	No	—
3	CRVO	HM	35	– –	½ closed	Mild	8	13	HM	18	–	½ closed	No	Pilocarpine
4	CRVO	HM	45	– –	¾ closed	Severe	6	7	NPL	53	–	Closed	No	—
5	CRVO	CF	47	–	¼ closed	No	2	10	HM	32	–	¼ closed	No	Pilocarpine
6	CRVO	CF	60	–	Closed	Severe	0	6	CF	19	–	Open, NV	No	—
7	CRVO	CF	38	–	½ closed	Mild	1	14	CF	14	–	Open	No	—
8	CRVO	HM	15	– –	Open, NV	No	6	15	NPL	16	–	½ closed	No	—
9	CRAO?	PL	52	– –	½ closed	Mild	6 years	8	NPL	30	–	½ closed	No	—
10	Diabetic retinopathy	6/12	17	– –	Open, NV	No	2 years	8	CF	15	–	Open	No	—

CRVO = central retinal vein occlusion, CRAO = central retinal artery occlusion, IOP = intraocular pressure, CF = counting fingers, HM = hand movements, PL = perception of light, NPL = no perception of light, NV = newly formed vessels.

(Fig. 1 A, B). Central visual acuity at the initial presentation, six weeks to eight months after the onset of symptoms, was poor in all cases (Table)—namely, hand movements (HM) in five eyes and counting fingers (CF) in three. At the latest examination the vision was unchanged in four eyes and had deteriorated in the others from CF to HM in one eye and from HM to no perception of light (NPL) in three.

Intraocular pressure (IOP) was raised in all but one eye with CRVO (case 8, Table) before photocoagulation, causing pain in five cases. Two eyes were painless in spite of raised IOP (56 and 47 mmHg respectively). After photocoagulation IOP decreased considerably in all but two cases. In case 8 IOP was also normal before treatment and in case 4 it remained unchanged because of complete angle closure. In the latter eye the pressure varied from 39 to 53 mmHg since treatment, but there was no discomfort in the eye and no other treatment was needed. In two cases pilocarpine drops were used after photocoagulation. The patient in one of these cases (case 5, Table) had chronic bilateral open-angle glaucoma. All eyes have been quiet and comfortable since photocoagulation.

Rubeosis iridis was present in all but one eye (case 7, Table), and in most cases neovascularisation was found both in the angle and around the pupil. Iris fluorescein angiography showed leakage of the dye from the new vessels (Fig. 2 A) and in some cases also from the radial vessels (Fig. 3 B). After photocoagulation clinically visible rubeosis decreased in all cases and in four eyes no new vessels could be seen. Iris fluorescein angiography showed persistence of new vessels in some cases, but there was less leakage of dye from the neovascularisation (Fig. 2 A, B) and also less congestion and leakage of the radial iris vessels (Fig. 3 A–D).

Both the initial appearance and the posttreatment findings in the chamber angle varied. In two eyes the angle was initially open in spite of new vessel formation (cases 1 and 8, Table), but both eyes developed some peripheral synechiae after treatment. In two cases (cases 2 and 6, Table) the angle was completely closed at the time of the acute rise of pressure. After treatment no permanent peripheral synechiae were found in case 6, and in case 2 synechiae closed less than half a circumference of the angle. In one eye with initially half-closed angle (case 7, Table) no rubeosis or synechiae were seen after photocoagulation, indicating the mechanism of acute angle closure attack in these cases. In two eyes (cases 3 and 5, Table) the amount of peripheral synechiae did not change after treatment, and in one eye (case 4, Table) the angle closed completely.

In case 9 (Table) rubeosis iridis and neovascular glaucoma had developed after presumptive central

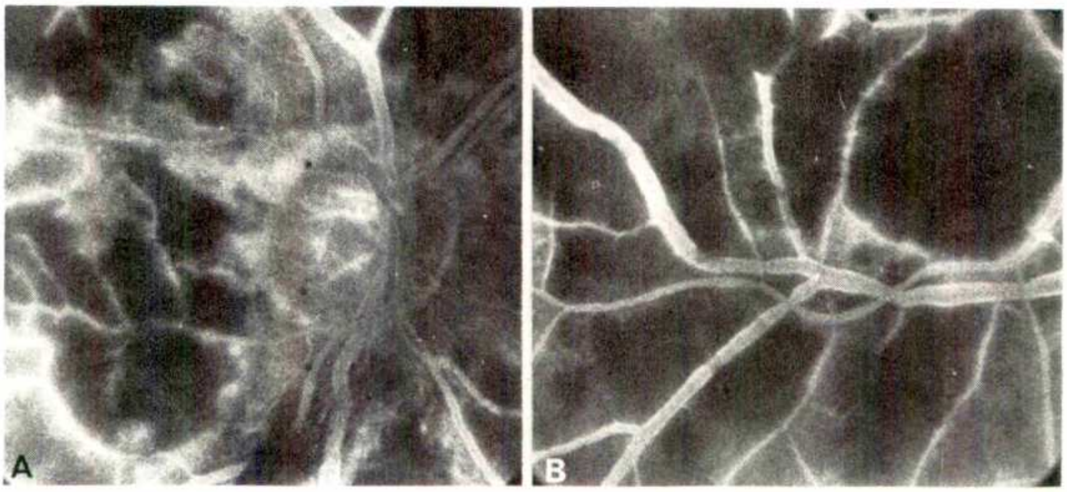

Fig. 1 *Case 6. Fluorescein angiogram of optic disc* (A) *and lower temporal area* (B) *showing complete capillary closure and leakage of dye from remaining vessels*

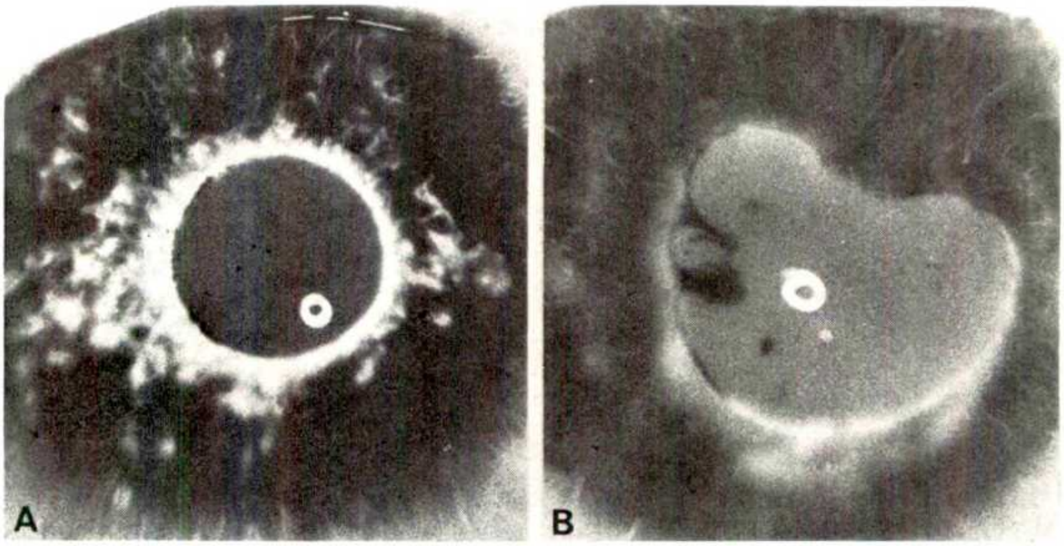

Fig. 2 *Case 8. Pretreatment iris fluorescein angiogram.* (A) *Considerable leakage from new formed vessels around pupil.* (B) *Same iris four months later after retinal photocoagulation, late picture. Mild fluorescein leakage but virtual obliteration of iris neovascularisation*

retinal artery occlusion six years before. This patient was, however, not seen at the acute stage, so possibly the acute episode was an ischaemic type of CRVO. The vision was perception of light only and the IOP varied from 31 to 52 mmHg. There was some transient pain although the eye looked quiet. Some rubeosis was seen on the iris, particularly in the chamber angle. Fluorescein angiography showed areas of neovascularisation and considerable leakage from the new formed vessels (Fig. 4 A, B). After retinal panphotocoagulation the IOP remained at about 30 mmHg and the eye was painless. There was no visible rubeosis, although some new vessels were still seen in the fluorescein angiogram (Fig. 4 C, D). The leakage, however, was less pronounced than it was before photocoagulation.

Case 10 (Table) represented an eye with diabetic

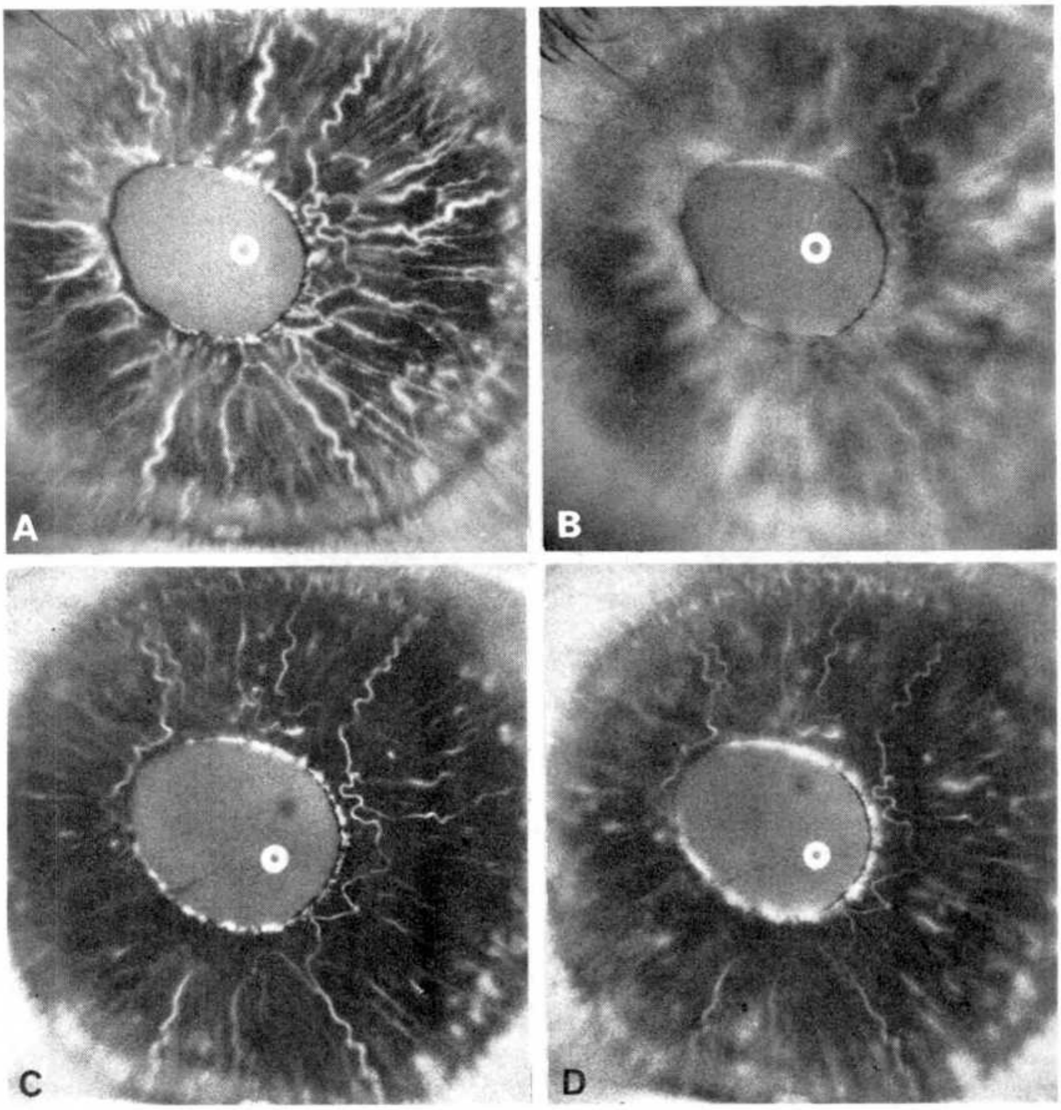

Fig. 3 *Case 5.* (A, B) *Pretreatment iris fluorescein angiogram. Dilatation of iris vessels* (A) *with remarkable leakage of dye* (B). (C, D) *Same iris one month after retinal photocoagulation. Considerably less congestion* (C) *and leakage* (D) *than before treatment*

retinopathy and optic disc neovascularisation. At the same time pronounced iris neovascularisation developed (Fig. 5 A, B). The anterior chamber angle was open, however, in spite of small new formed vessels crossing the angle, and the IOP was normal. Retinal panphotocoagulation was performed. Eight months after treatment iris neovascularisation was not clinically visible. Fluorescein angiography showed only remnants of the previous new vessels and these did not leak fluorescein (Fig. 5 C, D). The visual acuity of this eye subsequently deteriorated because of vitreous haemorrhage from persistent disc neovascularisation.

Discussion

Abnormalities in the iris vasculature after CRVO appear as abnormal vascular permeability associated with vessel dilatation or neovascularisation, or both (Raitta, 1968; Raitta and Vannas, 1969;

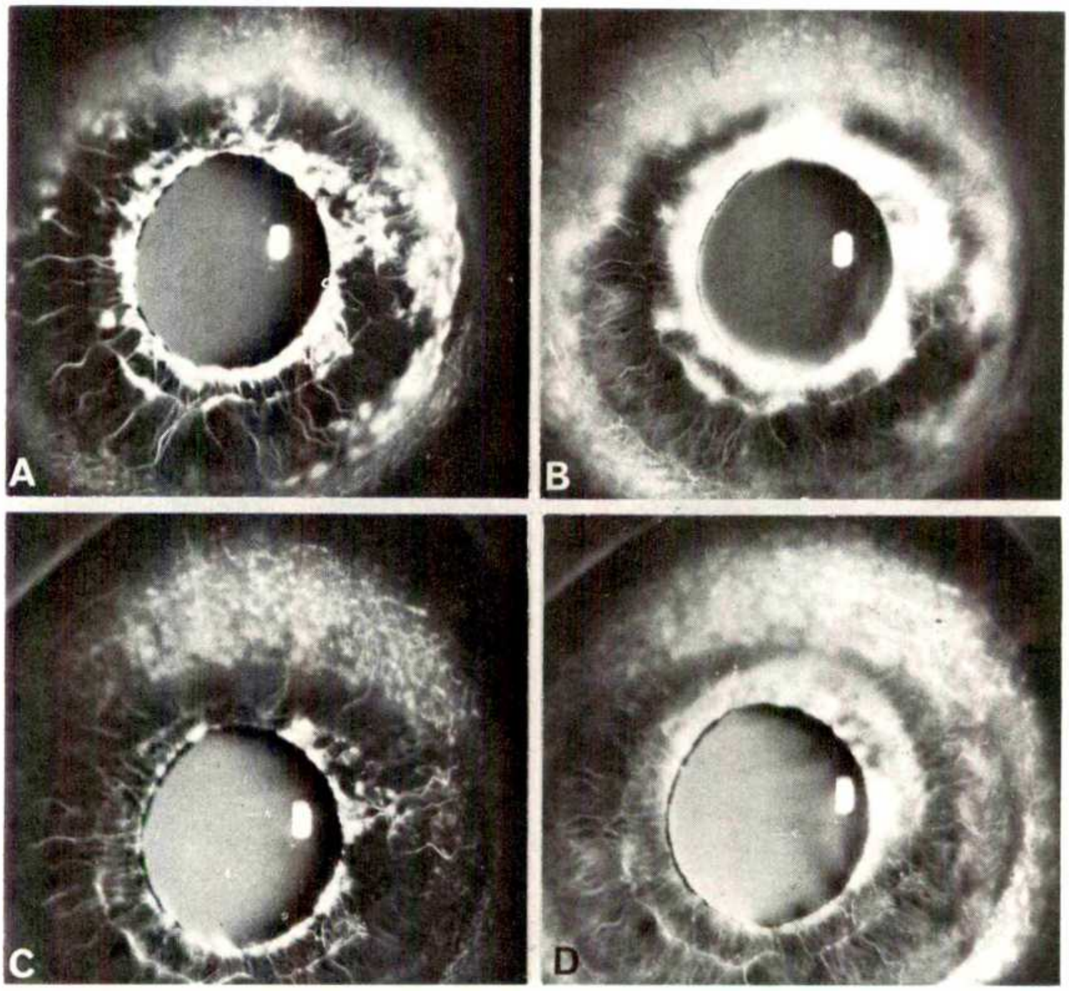

Fig. 4 *Case 9.* (A, B) *Pretreatment iris fluorescein angiogram. Considerable neovascularisation on pupillary margin and iris periphery* (A) *and leakage of fluorescein from new formed vessels* (B). (C, D) *Same iris one month after retinal photocoagulation. Considerable regression of rubeosis* (C) *and only mild leakage* (D)

Cappin and Whitelocke, 1974; Kottow, 1976; Laatikainen and Blach, in press). Venous congestion and abnormal permeability with or without capillary closure are also the main features in the retina in CRVO. Corresponding clinical studies on the vessels of the ciliary body have not been possible, but they may also be affected. As a result, the anterior chamber may become shallow and the angle closed after retinal venous occlusion even before iris neovascularisation develops. In three of the eyes an acute angle closure and a raised IOP were found before fibrovascular synechiae developed in significant amounts. Similar cases with an angle-closure attack precipitated by CRVO were described by Cappin and Whitelocke (1974).

After retinal panphotocoagulation abnormal leakage of both radial and new formed iris vessels decreased. In some cases iris neovascularisation was obliterated after treatment and in the others further progression of rubeosis iridis was prevented by photocoagulation. At the same time the IOP rapidly became normal in all the eyes in which the angle was not completely closed by anterior synechiae.

The stimulus for iris neovascularisation is not known. After CRVO more iris vessel changes develop in eyes with fundus neovascularisation (which is known to be caused by retinal capillary

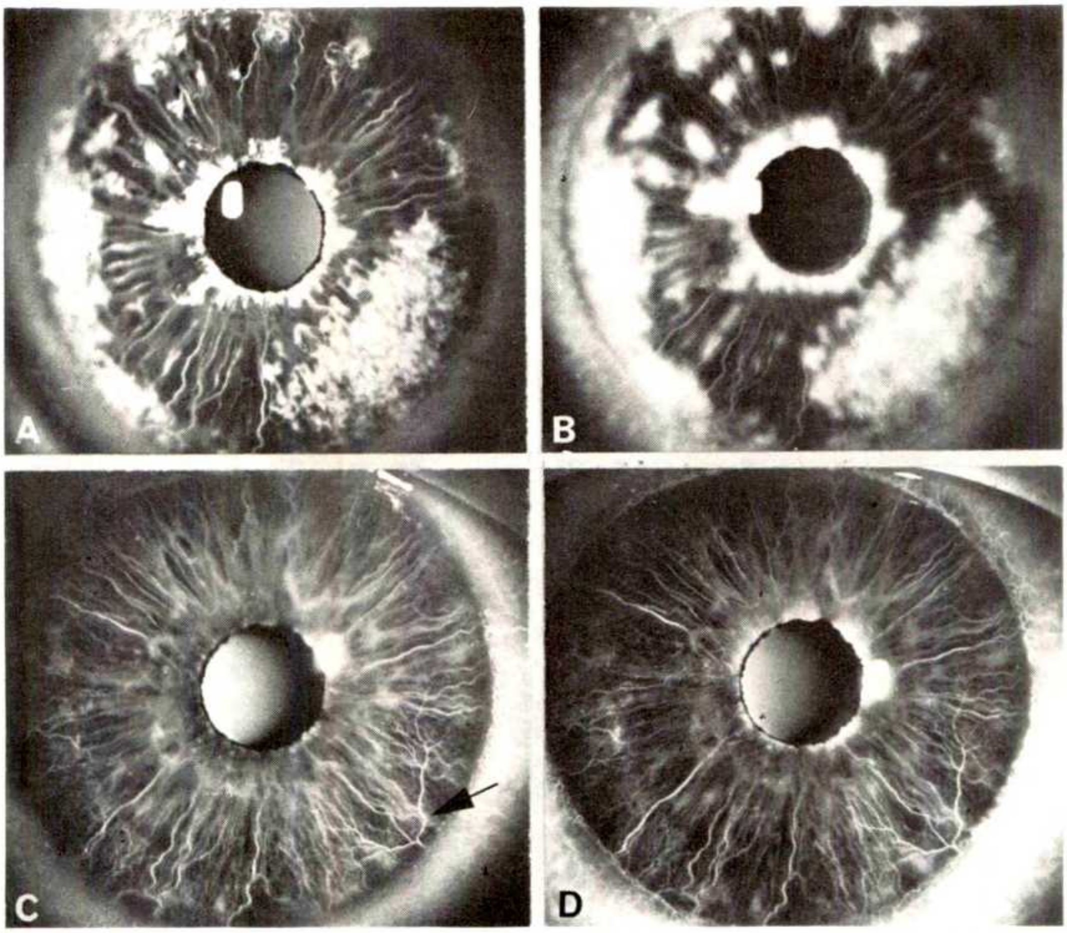

Fig. 5 *Case 10.* (A, B) *Pretreatment iris fluorescein angiogram. Extensive neovascularisation* (A) *and leakage of dye from new formed vessels* (B). (C, D) *Same iris eight months after retinal photocoagulation showing obliteration of neovascularisation* (C) *and virtually no fluorescein leakage* (D). *Some abnormal big vessel trunks still present on iris periphery* (arrow) *but do not leak fluorescein*

non-perfusion) than in those without (Kottow, 1976). In a recent fluorescein angiographic study we found a close correlation between iris changes and retinal capillary closure (Laatikainen and Blach, in press). These findings support the hypothesis that chronic retinal hypoxia is a cause of rubeosis iridis, as suggested by Ashton (1961) and Smith (1961). Retinal panphotocoagulation results in retinal atrophy instead of hypoxia and disappearance of the presumptive vasoformative stimulus. The post-treatment atrophy corresponds to that caused by acute central retinal artery occlusion or secondary arterial insufficiency and retinal atrophy spontaneously developing in many cases of diabetic retinopathy, or even in the ischaemic type of retinal venous occlusion in which iris neovascularisation sometimes disappears spontaneously.

Most of the treated eyes in the present series had initially very poor vision, and in some cases it deteriorated further during the follow-up. All eyes, however, have been quiet and painless since photocoagulation and most have not required any other therapy for neovascular glaucoma. These results suggest that photocoagulation may have a potential prophylactic and therapeutic role in rubeosis iridis and early neovascular glaucoma so long as the ocular media are clear and the pupil can be dilated.

I thank Mr R. K. Blach for supervising the study and advising on the preparation of the manuscript.

I am grateful to Mr K. S. Sehmi, who took most of the photographs.

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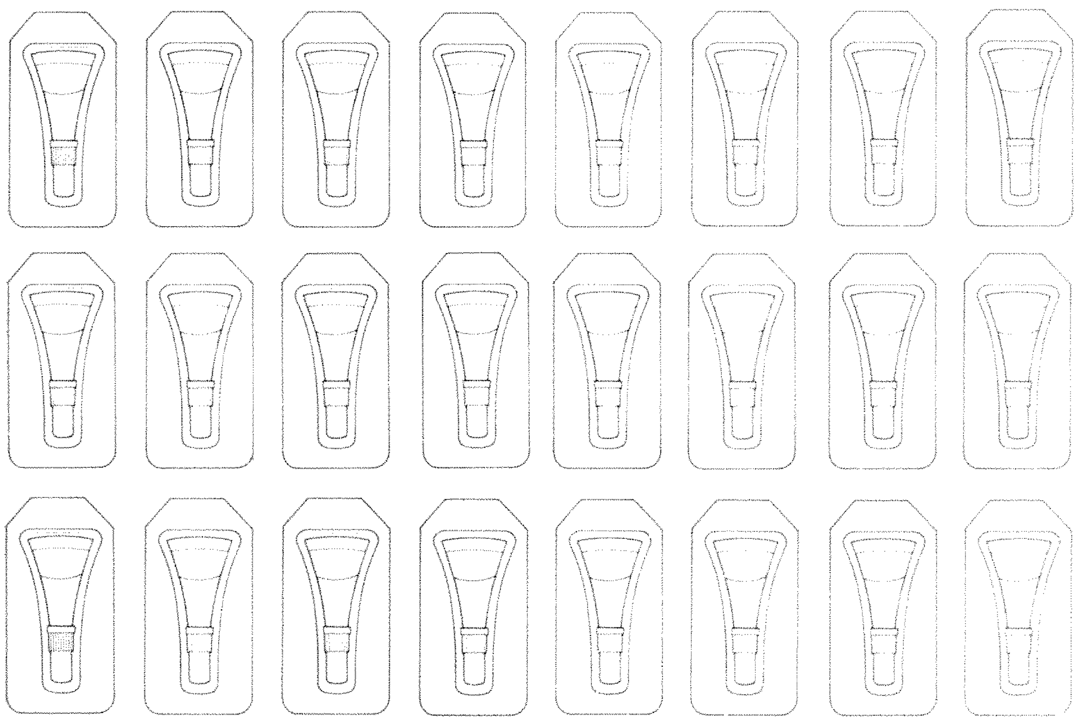

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Immunopathology of the lens

II. Humoral and cellular immune responses to homologous lens antigens and their roles in ocular inflammation

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SUMMARY It has been possible for the first time to demonstrate antibodies to homologous lens proteins in rabbits without the addition of adjuvant. By means of immunofluorescence and immunoperoxidase methods it has been possible not only to show for the first time that homologous lens antibodies cross-react with extraocular tissues but that the cross-reacting antigens are related to the cell mitochondria, microsomes, and the proteins associated with contractile organelles.

The rabbits did not produce antibodies to γ-crystallins even when the whole lens homogenate was injected with Freund's complete adjuvant. This suggests that γ-crystallins are non-antigenic in homologous situations, and this may be related to both B- and T-cell tolerance. Alternatively, the failure of γ-crystallins to induce antibody production may be due to intermolecular antigenic competition with other crystallins. The presence of mycobacteria in an adjuvant is essential for an antibody response to be detectable by agar diffusion techniques. The response to homologous lens antigens, both in magnitude as well as in duration, varied in different rabbits, which suggested to us that a central control mechanism involving the immune response (Ir) genes may play an important role. Antibodies to homologous lens proteins as detected by immunofluorescence and immunoperoxidase methods were shown to be of the IgG class. This is the first time that the kinetics of the immune response to the same homologous lens antigen in saline with or without incomplete or complete adjuvant has been examined and their relative merits compared.

Systemic homologous immunisation followed by discission of the lens led to a marked Arthus type reaction in and around the lens, but a typical granulomatous phakoallergic endophthalmitis was not produced. It seems likely that the rabbit is not suitable for the production of an experimental model of this condition.

It is now well established that the mammalian lens contains several soluble antigenic proteins (e.g., pre-α-, α-, β-, βs- and γ-crystallins) which can and do stimulate both antibody- and cell-mediated immune responses when animals are injected with lens proteins from unrelated species.

A positive humoral immune response to such heterologous lens protein was first demonstrated by Uhlenhuth (1903) and later confirmed by Hektoen (1922), Woods and Burky (1927), Manski *et al.* (1965), Clayton *et al.* (1968), and its study extended more recently by such techniques as immunofluorescence, immunoperoxidase, and lymphocyte transformation tests (Rahi *et al.*, 1977). Our latest studies have shown that the nature as well as the amplitude of the immune response varies in different animals largely according to whether the antigen is injected alone or with an adjuvant containing mycobacteria.

Since circulating antibodies can be induced without the incorporation of an adjuvant by repeated injections of large amounts of saline homogenates of heterologous lens, it had been speculated that an immune reaction to lens protein may lead to intraocular inflammation and formation of cataract. Since homologous rather than heterologous material is more likely to resemble autologous material, attempts were made to immunise animals with homologous lens proteins in order to study their effect on ocular tissues, but these experiments proved unsuccessful (Romer and Gebb, 1912; Morax and Pollack, 1914; Hektoen, 1922;

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Woods and Burky, 1930; Swift and Schultz, 1936). It was soon realised that the antigenic determinants on homologous lens proteins were not accessible to the immunologically competent cells unless the nature of these molecules was altered by chemical treatment. Thus Hektoen and Schulhof (1924) found that homologous lens proteins after fractionation with acetic acid induced an antibody response in rabbits. In a later study Woods and Burky (1930) confirmed this finding but stated that it is only the α-crystallin, the most acidic and heaviest of all the lens proteins, which after acid treatment becomes antigenic in homologous situations.

The antigenicity of the homologous lens protein has been re-examined by other workers, who found that saline homogenates of homologous lens antigen do not lead to any antibody response (Halbert and Manski, 1965; Manski, 1973). It is only when the homologous antigen is combined with Freund's complete adjuvant that the animals show any evidence of an immune response (Halbert *et al.*, 1957a, b). Furthermore, these workers also found that the antibody so raised did not cross-react with extraocular tissues of the rabbit, which is in contrast to the wide reactivity of the heterologous lens antibody (Halbert and Fitzgerald, 1958). The response to homologous lens antigens was later confirmed by Sourek and Klenka (1960). A review of the literature suggested to us that the following aspects of humoral and cellular immune responses to homologous lens antigens had not been adequately investigated.

Although it is widely held that homologous mammalian lens protein is nonantigenic when given without adjuvant, no serious attempt has been made to re-examine this aspect of the immune response of animals using such modern methods as immunofluorescence and immunoperoxidase labelling techniques.

Furthermore, we are not aware of any study in which the kinetics of the humoral immune response to the same homologous lens antigens in saline with or without incomplete or complete Freund's adjuvant have been examined and where the relative merits of agar precipitation, haemagglutination, immunofluorescence, and immunoperoxidase methods have been critically compared.

It is now known that the antibodies in man and other mammals belong to several distinct classes of immunoglobulins. It is also known that various serological techniques employed to detect specific antibodies to a given antigen demonstrate preferentially one class of immunoglobulin. For example, the agar precipitation test detects mainly high affinity IgG, the haemagglutination test mainly IgM, and complement fixation test only the complement fixing IgG and IgM. Immunoperoxidase and immunofluorescence methods on the other hand can, in addition, detect with equal efficiency other classes of immunoglobulins. By using monospecific antisera it should now be possible to be certain which immunoglobulin is mainly involved in homologous lens immunity.

It has only recently become clear that delayed tissue allergy is mediated by lymphocytes which are processed in the thymus and called T-lymphocytes. The delayed hypersensitivity can now be measured by a very precise *in-vitro* technique called the lymphocyte transformation test. So far as we are aware no such tests have been employed in the past to detect immune responses in animals injected with homologous lens proteins without any adjuvant. Since an immunological investigation would be incomplete without examining the T-lymphocyte reactivity, the assertion of Manski (1973) that homologous lens antigens on their own fail to induce an immune response needs further examination. Furthermore, we are not aware of any study in which the lymphocytes of animals sensitised with homologous lens antigens in saline, with or without incomplete or complete Freund's adjuvant, have been examined and the response correlated with antibody levels. Although cross-reactivity of heterologous lens antisera has been widely studied, adequate data on similar cross-reactivity of homologous lens antisera are lacking, and furthermore no attempt has been made at microscopical localisation of the cross-reacting antigen in ocular and extraocular tissues. The present study, therefore, was undertaken in an attempt to provide some answers to these problems and to bridge some of the gaps in our knowledge concerning the antigenicity of the homologous lens proteins, the nature of the immune response and its role in ocular inflammation.

Materials and methods

The study was performed on New Zealand adult albino rabbits using litter mates where possible. Rabbit total lens proteins in saline, with or without incomplete or complete Freund's adjuvant, were given intramuscularly at different sites at 10-day intervals. Each injection contained 15 mg of lens protein. The animals were bled on the first day of immunisation and also at the time of subsequent injections. After the final injection animals were skin-tested and the injection site was biopsied 48 hours later. They were anaesthetised and discission of the right lens was performed with a Ziegler's knife. They were killed a week later and blood was collected from the heart in preservative-free heparinised containers for lymphocyte transformation tests. Both eyes were enucleated for histological examination. Proper controls were set up as with the previous study on heterologous lens antigens (Rahi *et al.*, 1977).

Immunological investigations
The *Ouchterlony test* was performed in 1·5% agar in barbitone buffer (pH 8·2) at 4°C. The agar plates were washed 1 week later and after drying at 37°C were stained with 0·1% nigrosine.

Immunoelectrophoresis and *Osserman tests* were performed on 10 × 10 cm agar plates. The pH of the barbitone buffer in the agar was 8·2 (I=0·05) whereas in the electrophoresis tank it was 8·6 (I=0·075). The technique used was essentially the same as previously described (Rahi and Chignell, 1975).

The *passive haemagglutination test* was performed using formalised sheep red cells (Oxoid). These were first treated with 1:20000 analytical grade tannic acid solution in phosphate buffer saline (pH 7·2, 0·15 M) and then with homologous lens proteins which were previously adsorbed with untanned cells. The antigen concentration used was 2 mg for each millilitre of tanned sheep red cells. The cells thus sensitised were carefully washed with the buffer containing 1% normal rabbit serum which was previously heat-inactivated and preabsorbed. The final concentration of red cells was adjusted to 1·25%. The test was performed on a microtitre assay system (Cooke Laboratory). Controls were set up with sensitised red cells in buffer alone and with nonimmune serum obtained from the rabbits before initial immunisation. Controls were also set up using unsensitised cells with or without antiserum.

The *indirect immunofluorescence test* was performed using the standard technique. A Zeiss epifluorescence microscope equipped with an interference filter was used for the present study. Frozen sections of a composite block consisting of liver, stomach, kidney, parotid, and diaphragm from a rat and the stomach of a mouse were used to detect cross-reacting antibodies in homologous lens antisera. Rabbit, guinea-pig, and rat eye sections were used to detect an immune reaction not only with the lens but also with other ocular structures. The sera were tested at an initial dilution of 1:2 and both polyvalent (Wellcome) and IgG specific (Dako) anti-rabbit immunoglobulins labelled with fluoresceine (FITC) were used for the present study.

The *indirect immunoperoxidase test* was performed on frozen sections of the composite block and of the eyes as used for immunofluorescence examination. The sections were first treated with 1:20 normal pig serum and washed in phosphate buffer saline (pH 7·2) to inhibit non-specific reactions and then with 1:4 homologous lens antiserum. After washing in PBS with magnetic stirrer the sections were treated with 1:20 peroxidase-labelled anti-rabbit IgG serum (Dako) which was raised in pigs. The washed sections were incubated for 20 minutes in freshly prepared diaminobenzidine tetrahydrochloride (DAB) reagent in a concentration of 6 mg/10 ml Tris buffer saline and containing 2 drops of 10 vol solution of hydrogen peroxide. The sections were later washed in buffer and counterstained with haematoxylin.

Lymphocyte transformation test. The lymphocytes were separated from the rabbit blood by the Ficoll-Hypaque technique (Fotino *et al.*, 1971). One million lymphocytes were cultured in 1 ml T.C.199 (Wellcome) prepared in HEPES buffer and enriched with heat-inactivated 10% fetal calf serum. Several such cultures were set up in sterilin tubes. To each of the experimental tubes 0·1 ml of 1% sterile homologous lens solution was added followed 48 hours later by 2 μCi of tritiated thymidine (23 000 mCi/mmol Amersham). The control tubes, in which there was no lens protein, were similarly treated with the radioactive thymidine and incubated overnight. After centrifugation the proteins in the cellular deposits were precipitated with 5% trichloracetic acid and filtered on glassfibre filter paper which was washed in methanol and transferred into scintillation vials and air dried. 10 ml of a toluene-based scintillation fluid was added to each vial and the radioactivity was measured in a Packard tricarb liquid scintillation counter. The result was expressed as a transformation index, which represents the ratio of the radioactivity in the experimental tube to that in the control tube (i.e., E/C). In a positive reaction the transformation index is greater than 1.

Results

Serum collected from all rabbits immediately before immunisation was negative for lens antibodies as shown by the agar precipitation, haemagglutination, immunofluorescence, and immunoperoxidase tests. Antibodies to homologous lens proteins as shown by haemagglutination technique appeared on the 10th day of immunisation (though in low concentration) when the antigen was given with Freund's complete adjuvant. They appeared on the 20th day of immunisation when antigen was given with incomplete adjuvant, whereas when antigen was given in saline alone antibodies were not detectable until 30 days. The antibody concentration, however, was low.

The final homologous lens haemagglutinin titre in 1 rabbit 100 days after repeated immunisation rose to 1:20 480 with Freund's complete adjuvant.

Table 1 *Antibody response in a rabbit injected with homologous lens proteins in Freund's complete adjuvant*

Methods of antibody detection	*Days after initial immunisation*					
	10	*20*	*40*	*60*	*80*	*100*
Gel diffusion (Ouchterlony)	–	–	+	+	+	+
Immunoelectrophoresis	–	–	+ (α–β)	+ (α–β)	+ (α–β)	+ (α–β)
Passive haemagglutination	+ (1:10)	+ (1:40)	+ (1:640)	+ (1:2560)	*	+ (1:20 480)
Indirect immunofluorescence	±	+	+	+	*	+
Immunoperoxidase	*	+	+	+	*	+

+ Positive. ± Weak positive. – Negative. * Not tested. (α–β) = Antibodies to crystallins in α–β region

Table 2 *Antibody response in a rabbit injected with homologous lens proteins in Freund's incomplete adjuvant*

Methods of antibody detection	*Days after initial immunisation*					
	20	*30*	*40*	*60*	*80*	*>80*
Gel diffusion (Ouchterlony)	–	–	–	–	–	–
Immunoelectrophoresis	–	–	–	–	–	–
Passive haemagglutination	+ (1:30)	+ (1:30)	+ (1:50)	+ (1:320)	+ (1:160)	+ (1:160)
Indirect immunofluorescence	*	*	*	*	*	±
Immunoperoxidase	*	*	*	*	*	±

+ Positive. ± Weak positive. – Negative. * Not tested

Table 3 *Antibody response in a rabbit injected with homologous lens proteins without adjuvant*

Methods of antibody detection	*Days after initial immunisation*					
	30	*60*	*70*	*80*	*100*	*>100*
Gel diffusion (Ouchterlony)	–	–	–	–	–	–
Immunoelectrophoresis	–	–	–	–	–	–
Passive haemagglutination	+ (1:5)	+ (1:320)	+ (1:320)	*	+ (1:160)	+ (1:160)
Indirect immunofluorescence	*	*	*	*	+	+
Immunoperoxidase	*	*	*	*	+	+

+ Positive. – Negative. * Not tested

When the antigen was given either alone or with incomplete adjuvant the haemagglutinin titre was always very low. It rose temporarily to 1:320 on the 60th day but fell to 1:160 on the 100th day of immunisation (Tables 1, 2, 3). With complete adjuvant the lens haemagglutinin titre generally showed a sustained rise, but with incomplete adjuvant or when the homologous antigen was given in saline alone the plateau was reached much earlier. The kinetics of the immune response are shown in Fig. 1.

At least 3 precipitin lines were seen in Ouchterlony plates (Fig. 2) when serum from rabbits injected with homologous lens proteins in Freund's complete adjuvant were tested. Immunoelectrophoresis showed these lines in the α–β region. No precipitin lines were seen, however, when the antigen was given alone or with incomplete adjuvant. The level of the immune response was subject to individual variation even when the antigen was given with Freund's complete adjuvant. Thus 1 rabbit had a haemagglutinin titre of only 1:5 even after 14 weeks of repeated

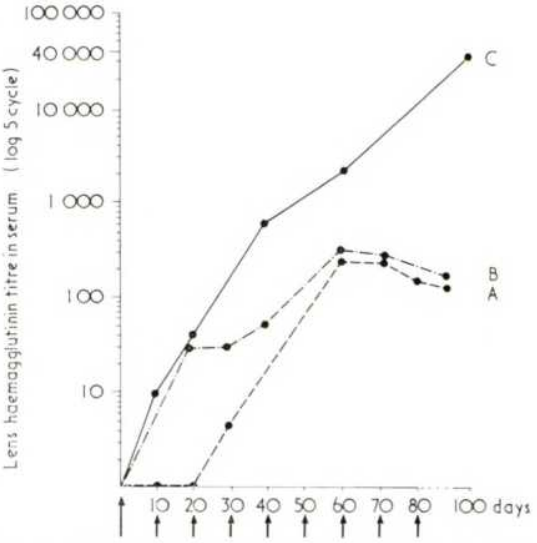

Fig. 1 *Kinetics of average antibody response in 3 groups of rabbits injected with homologous lens in saline* (A), *in incomplete* (B), *and in complete* (C) *Freund's adjuvant. The arrows represent immunising injections*

immunisation, whereas another rabbit similarly treated gave a titre of 1:20 480. In 1 rabbit the haemagglutinin titre after 100 days was 1:320 and remained stationary at that level even after repeated immunisation for another 50 days. The biological variations in homologous lens antibody responses are shown in Fig. 3 and Tables 4 and 5.

Immunofluorescence and immunoperoxidase tests were weakly positive for lens antibodies when sera from rabbits immunised with saline homogenate alone or with incomplete adjuvant were tested. A strongly positive result was obtained, however, when sera from animals injected with lens homogenate in complete adjuvant were used. These tests showed that homologous lens antibodies belong to the IgG class (Fig. 4). The possibility that they belong to the IgM class, however, and also to other classes cannot be excluded.

In addition to reactivity within the lens cortex sera from rabbits showing high-titre haemagglutinins showed weak cross-reactivity with the iris (Fig. 5), the ciliary body, the corneal epithelium, and the inner retina. Diffuse as well as coarse granular reactions were also noted with gastric parietal and chief cells, hepatocytes, and renal tubular epithelium

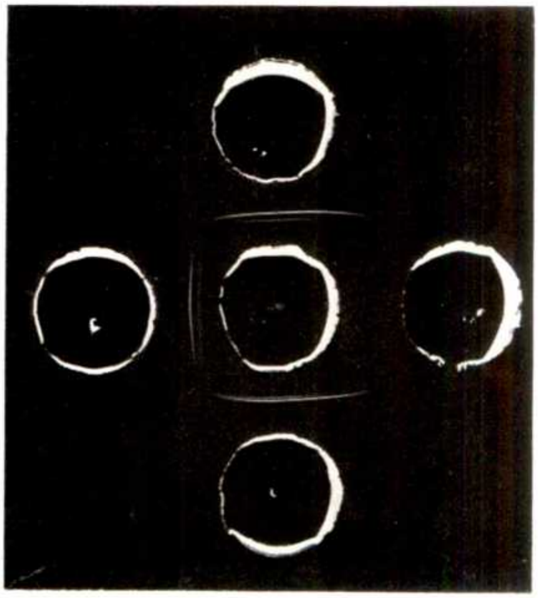

Fig. 2 *Ouchterlony test: The central well contains lens proteins from a rabbit. The peripheral wells contain sera from 4 rabbits immunised with homologous lens in Freund's complete adjuvant. There are a varying number of precipitin lines*

Table 4 *Biological variations in antibody response in a group of 7 rabbits injected with homologous lens proteins in Freund's complete adjuvant, 40 days after regular immunisation at 10-day intervals*

Methods of antibody detection	*Rabbits studied*						
	No. 1	*No. 2*	*No. 3*	*No. 4*	*No. 5*	*No. 6*	*No. 7*
Gel diffusion (Ouchterlony)	–	–	+	–	+	–	–
Immunoelectrophoresis	–	–	+ (α–β)	–	+ (α–β)	–	–
Passive haemagglutination	+ (1:60)	+ (1:30)	+ (1:640)	+ (1:5)	+ (1:640)	+ (1:40)	–
Indirect immunofluorescence	+	±	+	•	+	±	–
Immunoperoxidase	•	•	+	•	+	•	•

+ Postive. ± Weak positive. – Negative. • Not tested. (α–β) = Antibodies to crystallins in α–β region

Table 5 *Biological variations in antibody response n a group of 7 rabbits injected with homologous lens proteins in Freund's complete adjuvant, 100 days after regular immunisation at 10-day intervals*

Methods of antibody detection	*Rabbits studied*						
	No. 1	*No. 2*	*No. 3*	*No. 4*	*No. 5*	*No. 6*	*No. 7*
Gel diffusion (Ouchterlony)	−	−	+	−	+	−	−
Immunoelectrophoresis	−	−	+ (α-β)	−	+ (α-β)	−	−
Passive haemagglutination	+ (1:320)	± (1:320)	± (1:1280)	± (1:40)	+ (1:20 480)	+ (1:320)	± (1:5)
Indirect immunofluorescence	+	−	+	−	+	+	−
Immunoperoxidase	+	+	+	−	+	+	−

+ Positive. ± Weak positive. − Negative. * Not tested. (α-β) = Antibodies to crystallins in α-β region

(Figs. 6, 7). This suggests the presence of antimitochondrial, antiribosomal (and antimicrosomal) antibodies in homologous lens antisera, since a similar fluorescence has been described with human sera containing specific antibodies to mitochondria, ribosomes, and microsomes (Taylor *et al.*, 1962; Anderson *et al.*, 1967; Wright, 1975). A strong antiserum from one animal reacted with smooth muscle fibres in rat stomach, suggesting the presence of antibodies to contractile muscle proteins (Fig. 8).

The lymphocyte transformation test (T-cell reactivity) was strongly positive in a large proportion of the rabbits immunised with homologous total

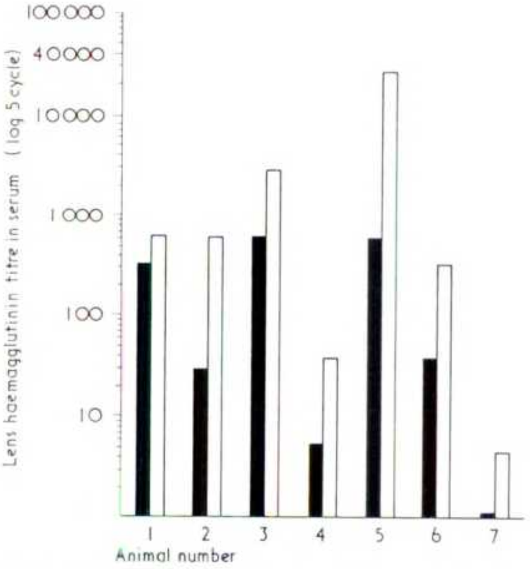

Fig. 3 *Biological variations in antibody response in 7 rabbits injected with homologous lens protein in Freund's complete adjuvant, 40 days (■) and 100 days (□) after regular immunisation at 10-day intervals*

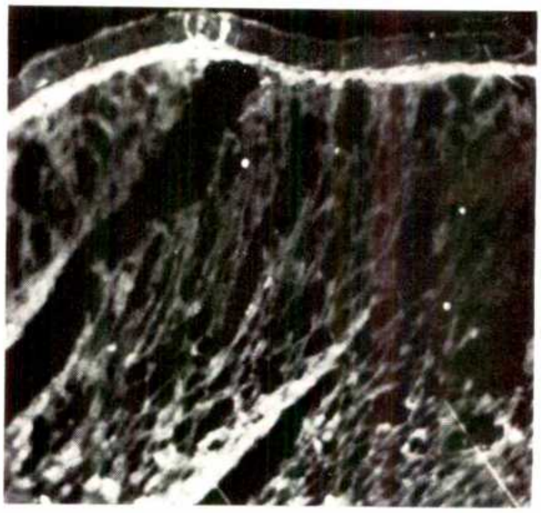

Fig. 4 *Indirect immunofluorescence test with an unfixed section of rat lens. Serum from an immunised rabbit reacts with the lens epithelium and the cortex to produce bright fluorescence. The fluorescein-labelled antiserum was IgG specific.* × 275

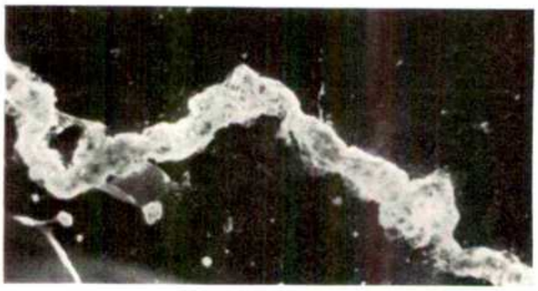

Fig. 5 *Lens antiserum containing cross-reacting antibodies. Note the fluorescence of rat iris.* × 350

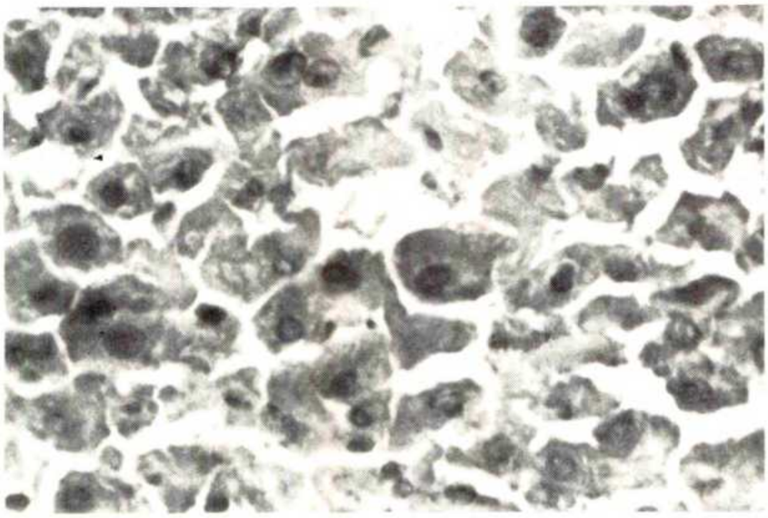

Fig. 6 *Indirect immunoperoxidase test with sections of the rat liver. Antilens serum reacts with the cytoplasmic contents (e.g., mitochondria and ribosomes) to produce dark reaction products. The nuclei have been counterstained with haematoxylin* × *900*

lens protein in Freund's complete adjuvant. The transformation index varied from 7 to 20 and generally correlated well with antibody titres as tested by agar precipitation and haemagglutination methods. The animals immunised with saline homogenate alone or in combination with incomplete adjuvant also showed evidence of T-cell reactivity. The mean transformation index was 2·5 and 3·5 respectively.

Skin biopsies from immunised rabbits following homologous lens injection showed a nongranulomatous reaction which consisted of lymphocytes, polymorphs, eosinophils, and macrophages (Fig. 9). The inflammatory reaction was more marked when antigen was given with complete rather than incomplete adjuvant. Animals which were injected with saline extract alone showed minimal infiltration. The needled eyes showed evidence of non-granulomatous inflammation. The lens was infiltrated with polymorphs, eosinophils, macrophages, and occasional lymphocytes and plasma cells (Fig. 10). A similar inflammatory exudate was present in the vitreous and also in the anterior chamber. The iris, however, showed only a mild inflammatory reaction. The eye from one of the rabbits immunised with homologous antigen in Freund's adjuvant, however, showed a fairly large number of plasma cells, lymphocytes, neutrophils,

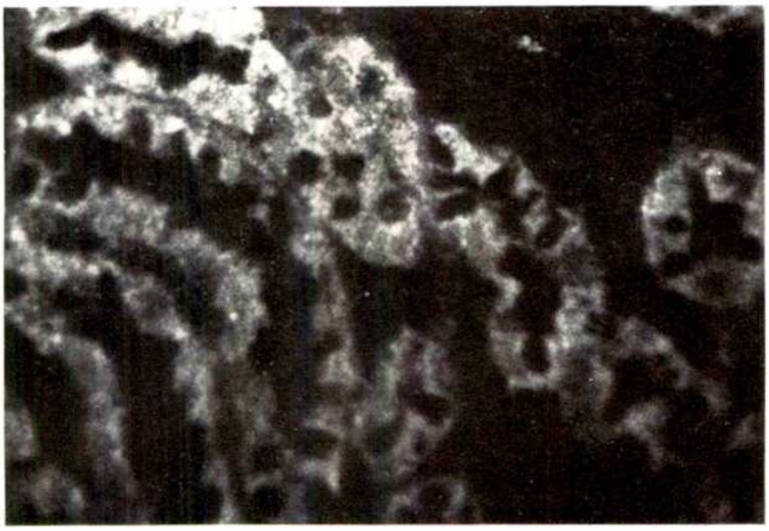

Fig. 7 *Lens antiserum containing antibodies to mitochondria and ribosomes. Note the bright granular fluorescence of some of the renal tubules. Indirect immunofluorescence test.* × *650*

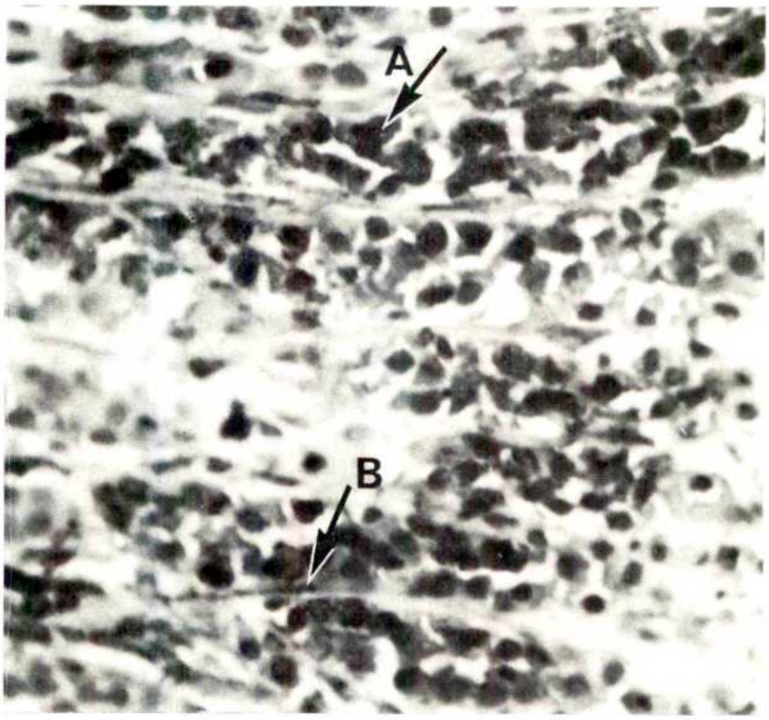

Fig. 8 *Indirect immunoperoxidase test with unfixed sections of the rat stomach. Lens antiserum from a rabbit reacts with the chief and the parietal cells* (A) *and the smooth muscle fibres between the glands* (B), *suggesting the presence of antibodies to mitochondria, ribosomes, and smooth muscle proteins. The nuclei have been counterstained with haematoxylin.* ×*900*

and eosinophils in the ciliary body (Fig. 11) and to a lesser degree in the iris. Epithelial hyperplasia of the lens (Fig. 12) with subcapsular fibrosis (Fig. 13) was a common feature of all eyes. As in the skin the reaction in the needled eyes of those animals where saline homogenates of homologous lens without any adjuvant were injected was minimal and consisted mostly of vasodilatation in the iris and the ciliary body.

Discussion

The present study has shown for the first time that homologous lens protein can induce a detectable

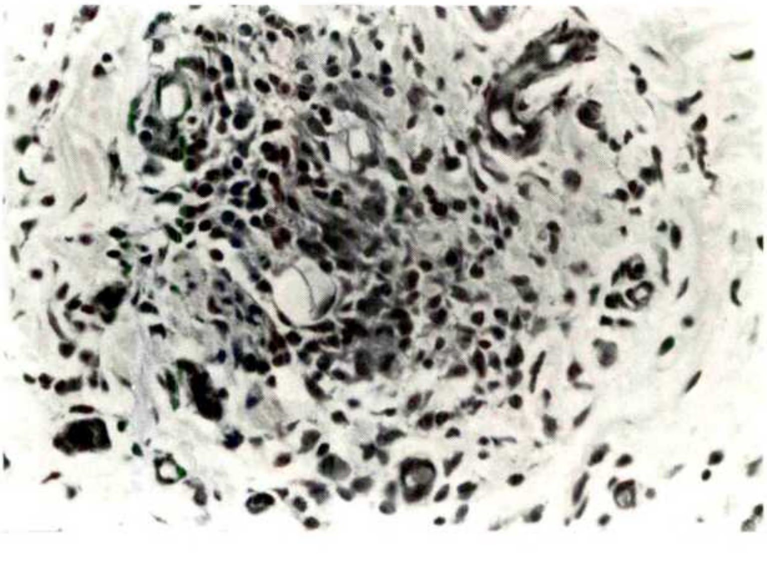

Fig. 9 *Section of the skin biopsy from an immunised rabbit injected with homologous lens protein. It shows an inflammatory reaction consisting of lymphocytes, polymorphs, eosinophils, and occasional macrophages. Haematoxylin and eosin.* ×*550*

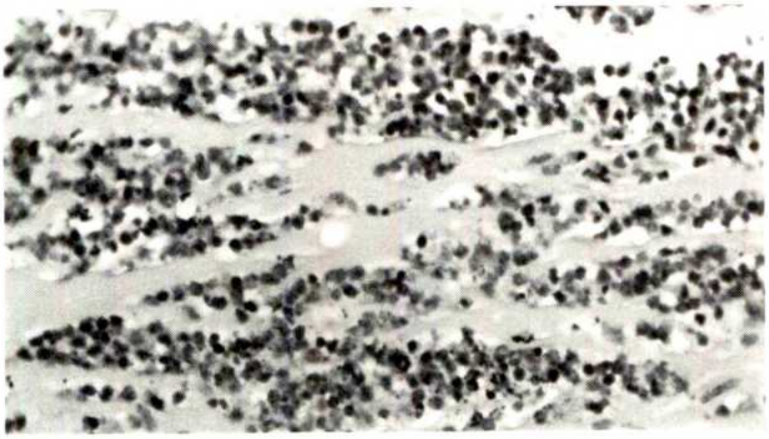

Fig. 10 *The needled lens of an immunised rabbit is diffusely infiltrated by degenerate polymorphs, eosinophils, macrophages, and occasional lymphocytes. Haematoxylin and eosin.* × *650*

immune response without the addition of any adjuvant. The degree of the immune response, however, was low and the specific antibodies were detected only by such sensitive techniques as the haemagglutination test. This is in contrast to heterologous lens proteins which induce an antibody response that can easily be detected by simple Ouchterlony and immunoelectrophoretic methods (Rahi *et al.*, 1977).

Although Halbert *et al.* (1957a, b) successfully demonstrated an antibody response to homologous lens proteins when injected with Freund's complete adjuvant, the present study has examined for the first time the role of adjuvant in the production of both cellular and humoral immune responses. It shows that both types of immune responses to homologous lens proteins in rabbits are much stronger when the antigen is given with Freund's complete adjuvant than when it is given alone or with incomplete adjuvant. It would appear, therefore, that in contrast to heterologous lens antigens the presence of mycobacteria is essential for a good humoral immune response to homologous lens proteins. This suggests that rabbits show a degree of immunological tolerance to lens proteins which can be overcome by using adjuvants rich in mycobacteria. Furthermore, since we failed to demonstrate any precipitating antibodies to γ-crystallins even when Freund's complete adjuvant was used, it seems probable that animals are tolerant to at least

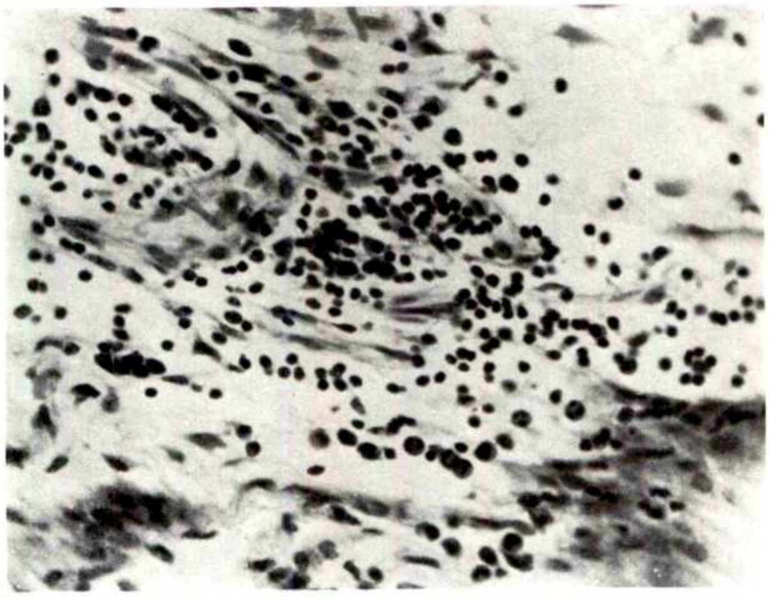

Fig. 11 *The ciliary body is infiltrated by eosinophils, lymphocytes and plasma cells. Haematoxylin and eosin.* × *650*

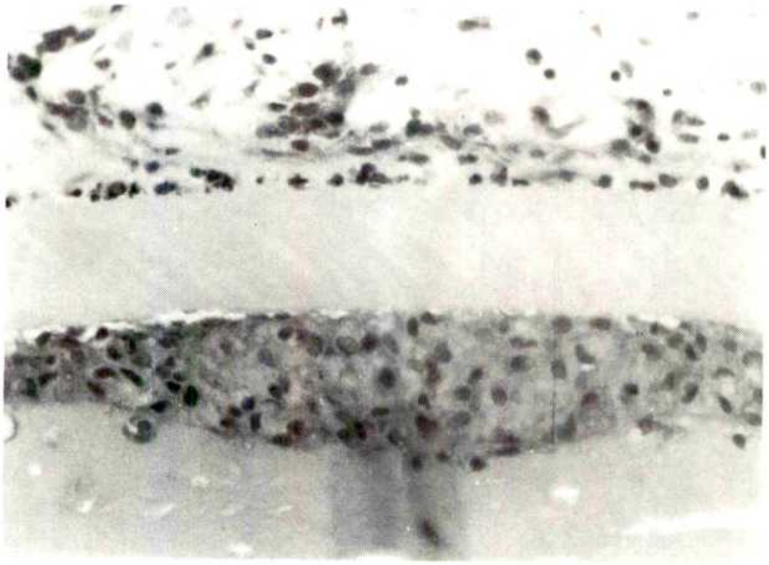

Fig. 12 *The needled lens of an immunised rabbit shows epithelial hyperplasia. Inflammatory cells surround the lens capsule. Haematoxylin and eosin.* × 550

these homologous lens proteins. The reason why rabbits react to heterologous but not to homologous γ-crystallins may be related to some differences in the antigenic determinants and their accessibility to the immune system. It would appear that, so far as homologous γ-crystallins are concerned, rabbits probably show a state of tolerance which is likely to involve both B- and T-lymphocytes. This subject has been discussed in detail in our earlier study on heterologous lens proteins, and although in most textbooks lens proteins are still considered to be sequestrated antigens, which means that animals should be intolerant to all of them (i.e., α-, β-, and γ-crystallins) and should be able to produce antibodies without the addition of adjuvants, there is now evidence that they are probably tolerant to homologous γ-crystallins as evinced by the conspicuous absence of γ-precipitin lines in the immunoelectrophoretic study. It is possible, however, that the absence of an immune response to homologous γ-crystallins was due to an intermolecular antigenic competition (Michaelis, 1902) because of

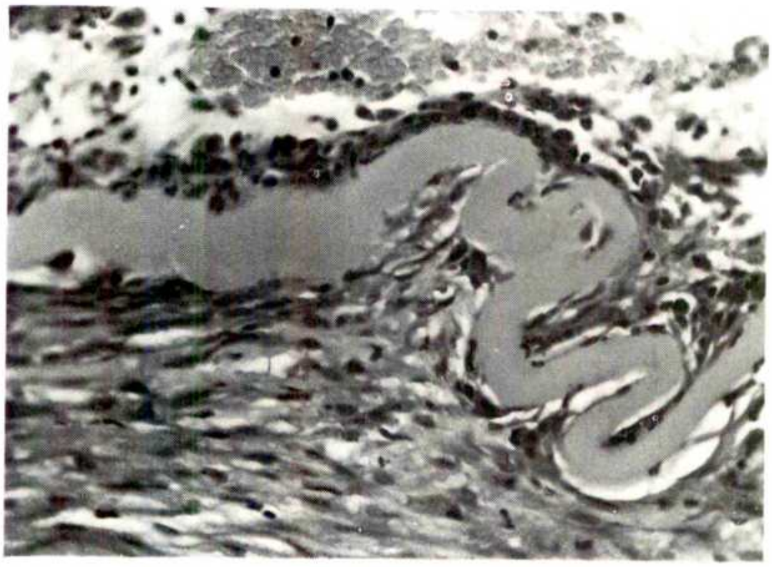

Fig. 13 *Sections show an injured lens with marked subcapsular fibrosis and extracapsular inflammatory cells. Haematoxylin and eosin.* × 550

the presence of α- and β-crystallins in the injected lens homogenate. It is now known that the inhibition of the immune response to one antigen by the simultaneous administration of another antigen is T-lymphocyte dependent and is probably related to the antigen specific T-cell products which through the agency of macrophages play a decisive role in the activation of B-lymphocytes which eventually transform into antibody-producing plasma cells (Taussig, 1975).

The kinetics and the variability of the immune response studied in several groups of animals further emphasises the role of immunological tolerance. It is known that the immune responsiveness to a variety of antigens is controlled by the immune response (Ir) genes, which are associated with the major histocompatibility region of the chromosome (Ellman *et al.*, 1971). Furthermore, it seems likely that mycobacteria present in the complete adjuvant modify the response to homologous lens proteins possibly by their direct non-specific effect on the T-lymphocytes. This effect, however, does not seem to influence the response to γ-crystallins, but this requires further critical examination.

A comparative study of the 5 different methods for the detection of homologous lens antibodies, which have been performed for the first time on the same serum sample, shows clearly that the best method for detecting antibodies to lens proteins is the passive haemagglutination technique, which becomes positive before the other tests. For reproducible results, however, it is necessary to use freshly homogenised lenses, which should be preadsorbed with sheep red cells before the lens homogenates are used to coat the tanned red cells. The serum to be tested should be preabsorbed and heat-inactivated immediately before the test.

Immunofluorescence and immunoperoxidase tests are less sensitive. Ouchterlony and immunoelectrophoretic techniques are least sensitive, being positive only when the homologous lens haemagglutinin titres were 1:640 or more. The one advantage of the immunoelectrophoretic technique, however, was in its capacity to demonstrate that antibodies to homologous γ-crystallins did not appear even when the whole lens solution was injected with Freund's complete adjuvant. The immunofluorescence and immunoperoxidase tests had one advantage over the haemagglutination and the immunoelectrophoretic tests in being able to detect the chemical class of the immunoglobulin involved in an immune reaction to homologous lens proteins. It is now possible, therefore, to state with certainty that IgG is involved in this reaction, although it does not exclude the possible role of other immunoglobulins.

Although Halbert and Fitzgerald (1958) failed to detect by agar diffusion techniques any cross-reactivity between homologous lens antisera and extraocular tissues, our study, using much more sensitive methods of immunofluorescence and immunoperoxidase, show clearly not only that such cross-reactivity exists but that the cross-reacting antigens are related to mitochondria, ribosomes, and the proteins associated with contractile organelles. It is of interest that the lens epithelium and the superficial lens fibres contain all or most of these organelles (Hogan *et al.*, 1971). Furthermore, these organelles, although not discernible electron microscopically in the deeper regions of the lens, might be present in inspissated structureless forms. That this may be so is supported by the evidence that ribonucleoproteins can be extracted from the lens nucleus (Maraini *et al.*, 1964).

The reason why we obtained a higher lymphocyte transformation index with homologous immunisation as compared to our previous heterologous study is probably related to the fact that in the present study the rabbits were injected with total lens extract instead of soluble proteins only.

Systemic immunisation with homologous lens protein followed by discission of the lens did not lead to a granulomatous phakoallergic endophthalmitis.* The lenses, however, were infiltrated by polymorphs, eosinophils, lymphocytes, and plasma cells, suggesting an Arthus-type reaction. The lens epithelial hyperplasia and subcapsular fibrosis which were found in almost every eye were produced either by injury or perhaps as a result of an immune reaction analogous to that which leads to the formation of a retrocorneal membrane in a failed graft.

The fact that a granulomatous reaction was not present in spite of marked delayed hypersensitivity, as evinced by a strongly positive lymphocyte transformation test, suggests that the rabbit is not a suitable experimental model for lens-induced uveitis. Furthermore, this is borne out by the fact that in spite of a marked cellular infiltration in and around the injured lenses, the iris and the ciliary body showed only a minimal inflammatory reaction. Goodner (1964) immunised rabbits with homologous lens antigens in Freund's complete adjuvant and similarly failed to demonstrate typical lens-induced uveitis even when lens material was injected into the vitreous of the previously sensitised animals. In a study using heterologous and homologous lens antigens we have found that guinea-pigs and rats show a greater propensity to develop phakoallergic endophthalmitis. These studies will be reported in detail elsewhere.

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*The term phakoallergic endophthalmitis has been used throughout the text as a preferred alternative to such terms as lens-induced uveitis, endophthalmitis phako-anaphylactica or phakogenic endophthalmitis. The reasons for this are discussed in a separate communication.

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Trabeculotomy in pseudoexfoliation of the lens capsule

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SUMMARY Trabeculotomy was performed on 12 eyes of 11 patients with glaucoma associated with pseudoexfoliation of the lens capsule. Pressure was lowered in all eyes, in 10 eyes to 15 mmHg or less, 7 with no medication but 3 with medication. A subconjunctival bleb was present in 5 patients but was not necessary for a good result. These results suggest that the raised intraocular pressure which often occurs in pseudoexfoliation of the lens capsule is due to interference with flow of aqueous across the trabecular meshwork. Trabeculotomy seems a safe and effective operation in glaucoma associated with pseudoexfoliation of the lens capsule.

Pseudoexfoliation of the lens capsule is a condition in which there is a high incidence of glaucoma. There is also a deposition of pseudoexfoliative material and pigment in the trabecular tissue at the angle of the anterior chamber. Does the deposition of this material cause an increase in resistance to the flow of aqueous into the canal of Schlemm with a rise in the intraocular pressure? If it does, then the surgical operation of trabeculotomy, which divides the trabecular tissue between the anterior chamber and the canal of Schlemm, may lower the intraocular pressure. This paper reviews a group of patients with glaucoma and pseudoexfoliation of the lens capsule on whom trabeculotomy was performed.

Material and methods

The surgical operation of trabeculotomy was performed on 12 eyes of 11 patients all with glaucoma associated with pseudoexfoliation of the lens capsule. The operation was performed on eyes with progressive field loss in the presence of an intraocular pressure which could not be controlled to less than 20 mmHg by full medical therapy. Patients were followed up for periods of 6 months to 3½ years postoperatively.

Trabeculotomy was performed after the method of Harms and Dannheim (1969), and Dannheim (1972). The conjunctiva was reflected. A half thickness scleral flap 3 × 3 mm based on the limbus was raised and a linear incision made down to the canal of Schlemm. Trabeculotomy probes were then passed for about 60° along the canal of Schlemm to either side and rotated into the anterior chamber. The scleral flap was sutured back in place with 7 or more 10·0 nylon sutures and the conjunctiva was closed. The anterior chamber was not lost throughout the procedure, and the wound was watertight at the conclusion of surgery.

Results

The intraocular pressure was lowered in all the eyes (Table 1). In 10 eyes the pressure was lowered to 15 mmHg or less, in 7 without any treatment and in 3 with the help of medical treatment. Of the 7 eyes with a pressure of 15 mmHg or less with no treatment 4 had a subconjunctival drainage bleb and 3 did not. One other eye with a bleb needed miotic drops to attain a pressure of 20 mmHg.

In all patients gonioscopy showed a cleft present in the region of the canal of Schlemm. This cleft seldom extended over the full extent of the trabeculotomy and tended to extend forwards towards Schwalbe's line as if the trabecular tissue had disinserted from this line. Reflux of blood from the ruptured canal of Schlemm into the anterior chamber was seen gonioscopically in 6 of the 12 eyes; in 2 of these eyes miotic drops were necessary to get a satisfactory intraocular pressure.

There were no serious complications in any of the eyes. A small hyphaema was common postoperatively but cleared before the patients went home in 5 days. Some peeling of Descemet's

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Table 1 *Results of trabeculotomy in glaucoma with pseudoexfoliation of lens capsule*

Patient	*Sex*	*Age*	*Follow-up (months)*	*Pressure Preop* *No R_x*	*Pressure Preop* *On R_x*	*Pressure postop*	*Bleb*	*Reflux of blood*
1	F	76	42	28	26	15 (R_x)	No	–
2	M	67	37	43	30	12	No	–
3	F	56	37	50	28	11	Yes	–
4	M	73	37	37	27	9	Yes	
5	F	65	26	28	22	11	No	
6	M (R)	65	23	43	20	15	Yes	
	(L)		23	43	34	20 (R_x)	Yes	–
7	F	59	22	43	26	14	No	–
8	F	71	18	35	25	12 (R_x)	No	–
9	M	70	13	58	28	16	No	–
10	F	78	8	40	26	14	Yes	–
11	M	71	6	32	25	11 (R_x)	No	

Preop = Preoperative pressure.
Postop = Postoperative pressure.
R_x = Medical treatment
Patient 6 had both eyes operated on.
F = Female.
M = Male.

membrane in the region of the operation was common but caused no ill effects. There were no flat or shallow anterior chambers postoperatively. The anterior chamber was not lost at operation in any case. In 2 eyes the pressure has become more difficult to control with lapse of time since the operation.

Comment

Trabeculotomy is a safe and effective operation for glaucoma associated with pseudoexfoliation of the lens capsule. First described by Burian (1960) and Smith (1960), it attempts to remove the resistance to aqueous flow across the trabecular meshwork. Its success in this type of glaucoma suggests that the deposition of pseudoexfoliative material and pigment in the trabecular meshwork causes a rise in the trabecular resistance to aqueous flow, with a consequent rise in intraocular pressure.

Whether the deposition of pseudoexfoliative material and pigment causes a rise in intraocular pressure in a particular eye probably depends on the pre-existing state of the trabecular meshwork. Patients with a very low resistance to aqueous outflow are unlikely to develop a rise in intraocular pressure, while those with a marginal resistance are more likely to do so. As resistance to aqueous outflow may vary between two eyes in a patient, it occasionally happens that one eye with clinical pseudoexfoliation will have a normal intraocular pressure while the other with no pseudoexfoliation will have a raised intraocular pressure.

The presence of a subconjunctival bleb was not necessary for a successful result, though it was common among eyes with a good result. Although great care was taken to secure watertight scleral closure, it seems inevitable that subconjunctival leakage of aqueous will occur in some eyes once trabecular resistance is removed. The presence of a reflux of blood from the trabeculotomy site in 6 eyes is strong evidence that a communication has been established between the canal of Schlemm and the anterior chamber. As blood filling of the canal of Schlemm does not always occur at gonioscopy, blood reflux from the region of the trabeculotomy cannot be expected in every eye, even if the trabeculotomy is patent. Not all patients with reflux of blood from the trabeculotomy site achieved a low intraocular pressure without miotic drops.

The use of miotic drops lowered the intraocular pressure if it was still raised, though miotic drops are commonly thought to act by the way of the pull of the scleral spur on the trabecular tissue. Possibly they act after trabeculotomy by opening the trabeculotomy cleft.

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Episcleral traumatic conjunctival inclusion cyst

ROBERT Y. BARISHAK, E. BARUH, AND M. LAZAR

From the Mitrani Foundation Eye Pathology Laboratory, the Chaim Sheba Medical Center, Tel Hashomer Hospital, and the Department of Ophthalmology, Ichilov Hospital, both affiliated to the Sackler School of Medicine, Tel Aviv University, Israel

SUMMARY A huge episcleral traumatic conjunctival inclusion cyst enveloping almost the whole eye, which appeared in the left phthisical eye of a young woman who sustained a perforating ocular injury a few years before enucleation, is described.

Intrascleral traumatic implantation cysts are rare. Usually they are formed by the conjunctival epithelium. This rarity is explained by the inadequacy of the scleral tissue to act as a culture medium for the epithelial cells (Duke-Elder and MacFaul, 1972). But the episclera should not impede the conjunctival epithelium from proliferating and forming cysts; indeed, superficial conjunctival inclusion cysts appear frequently in the episcleral plane after penetrating injuries. Epithelial implantation cysts which penetrate in the episcleral plane deep to the optic nerve at the posterior pole and surround almost the whole eye have not been so far reported. Our case exemplifies such a possibility.

Case report

A 33-year-old female sustained in 1970 a perforating injury of the left cornea in a road accident. She underwent suturing of the cornea, and the visual acuity decreased to light perception only. A few months later, a limbal staphyloma appeared inferiorly and increased steadily. Later the patient started to complain of severe pain in this eye, which lost its light perception. She was admitted for enucleation.

On admission of the patient the right eye appeared normal. The left eye presented ciliary injection, a vertical linear scar in the cornea with Descemet folds, and a total iris coloboma inferiorly covered by a pupillary membrane. Inferiorly a large limbal staphyloma extended along the inferior limbus and pushed the cornea upwards. On 26 January 1976 enucleation of the left eye was performed. With the opening of the conjunctiva at the limbus a huge scleral cyst was discovered inferiorly at the site of the staphyloma. The eye was removed together with the cyst.

MACROSCOPY

The left eye was phthisical (22 × 20 × 20 mm) and soft on palpation. A huge cyst was present inferiorly between the sclera and the thickened episclera. The opening of the cyst was 14 × 15 mm in size (Fig. 1). Vertical section showed that a cystic space was present not only inferiorly but also superiorly and temporally, and that it extended to the optic nerve (Fig. 2). The retina was totally detached, funnel-shaped, and adherent anteriorly to a thick cyclitic membrane. The cornea was leucomatous and heavily vascularised.

MICROSCOPY

The outer surface of the sclera (Fig. 3) and the inner face of a thickened episclera were lined with a stratified multilayered epithelium showing a

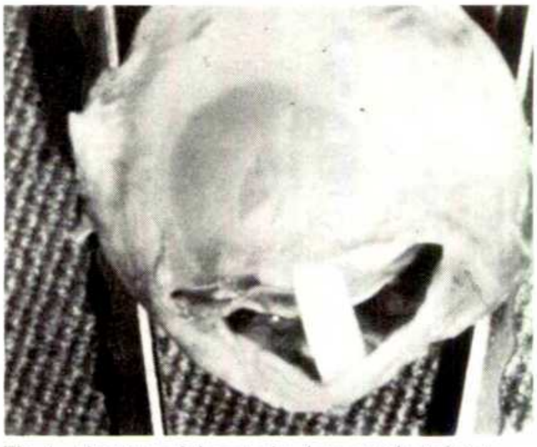

Fig. 1 *Opening of the episcleral cyst at the inferior limbus*

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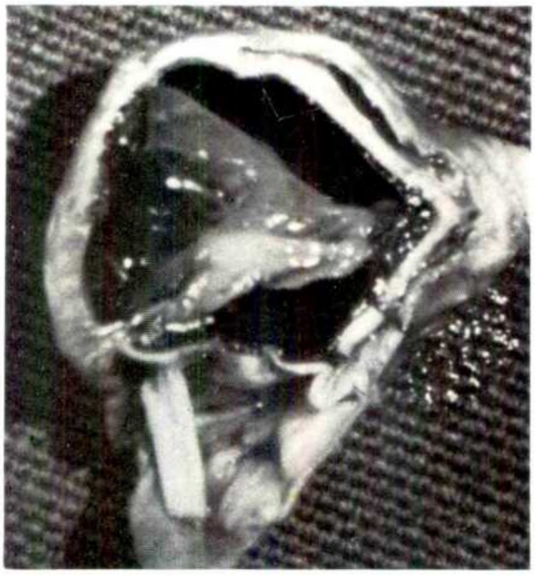

Fig. 2 *Cystic space present superiorly and inferiorly between the sclera and the episclera and extending to the posterior pole. The retina is totally detached*

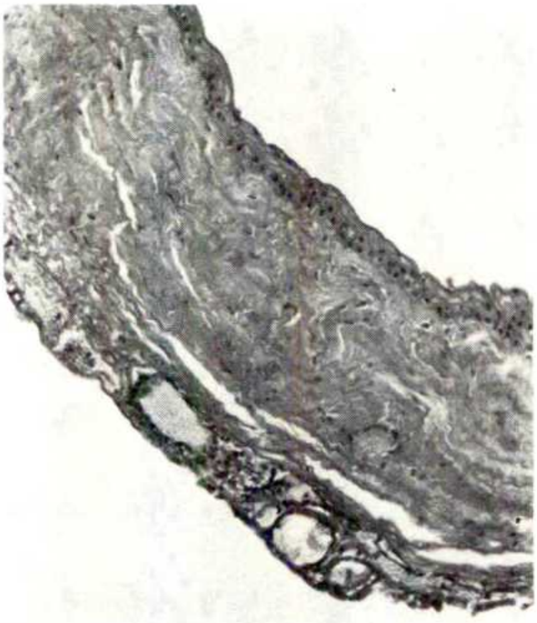

Fig. 3 *Choroid and sclera covered by a moderately keratinised epithelium.* × *120*

moderate keratinisation (Fig. 4) and extending to the posterior cul-de-sac (Fig. 5). Some amorphous substance was present in the lumen, apparently debris from the epithelial lining. There were foci of non-specific chronic inflammation in the sclera and episclera.

Discussion

At operation this cyst was considered to be an intrascleral cyst. Histological examination showed that it was located at the level of the episclera. The episclera, a loose connective tissue, does not impede the proliferation of the conjunctival epithelium and can give way before such a large extension to the conjunctival invagination. We termed the cyst episcleral and not intrascleral in view of the histological characteristics. The location of the cyst was remarkable. Traumatic implantation cysts are usually found anteriorly in the exposed parts of the

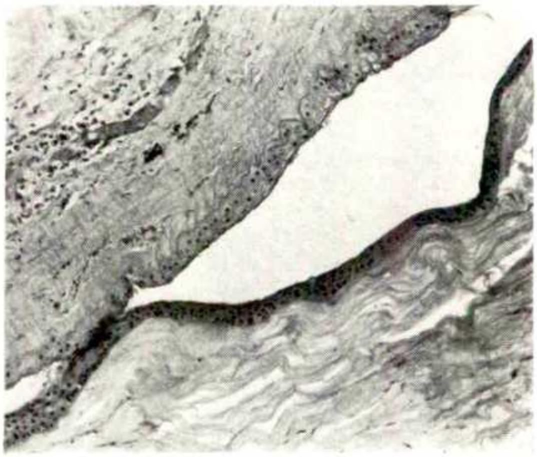

Fig. 4 *Both walls of the cyst covered by a moderately keratinised epithelium.* × *95*

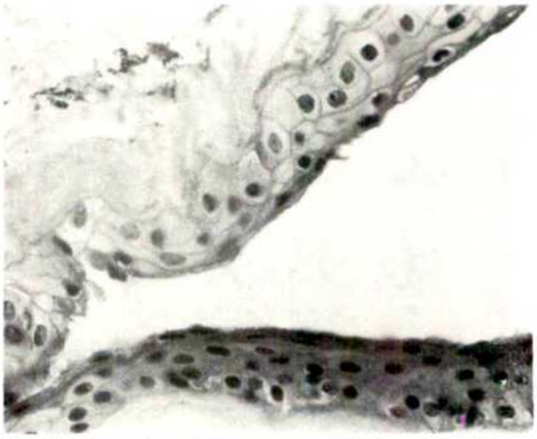

Fig. 5 *Posterior cul-de-sac covered by keratinised epithelium.* × *390*

sclera, near the limbus or a little posterior to it, under the bulbar conjunctiva (Ischreyt, 1907). They increase slowly in size, with a thin outer wall; the cyst becomes soft and even appears bluish (Eisenstein, 1907), as was the case with our patient. The limbus is a natural barrier for its extension anteriorly and often the cyst tends to encircle it (Gruening, 1900–02). In our case it extended along the whole inferior limbus. However, the most remarkable feature of this cyst was the fact that it surrounded at least three-quarters of the outer surface of the eyeball and also part of the distal portion of the optic nerve. This was the feature that prompted us to publish the case.

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Book reviews

Practical Ophthalmic Plastic and Reconstructive Surgery. By M. J. Reeh, C. K. Beyer, and G. M. Shannon. 1976. Pp. 203, figs., refs. Lea & Febiger, Philadelphia (Henry Kimpton, London) (£15·95)

All self-respecting plastic surgeons have a method of their own for tackling problems in reconstruction, and though the hairs of their heads may be numbered it is unlikely that the same can be said for their permutations and combinations. For the ophthalmic surgeon there is therefore a crying need for a simple book clearly written and illustrated describing well-tried plastic procedures for conditions affecting the eyes and their adnexa. This book is just such a treatise, consisting of 200 pages liberally illustrated with photographs and backed up by excellent line diagrams. The authors are fortunate in having the support of the classical work of Lester Jones and Margaret Obear. It is a text to be read and kept for reference. Like the *A to Z* street-plan of London or the map of the underground subway, the reader should keep it handy when about to explore fresh territory or revisit a half-forgotten area.

The titles of the chapters give an adequate prospectus of the ground covered—Anatomy and Physiology, Basic Principles, Preoperative Evaluation, Tumour Evaluation, Eyelid Reconstruction, Surgery of the Canthus, Blepharoptosis, Malpositions of the Eyelids (Entropion and Ectropion), Blepharoplasty, Lachrymal System, Conjunctival Surgery, and The Orbit (Enophthalmos, Exophthalmos, Orbital Fractures, Exenteration).

STEPHEN MILLER

Wolff's Anatomy of the Eye and Orbit. By R. Warwick. 1976. Pp. 536, figs. 467, tables, refs. H. K. Lewis, London (£13)

This book—'Eugene Wolff's Anatomy of the Eye and Orbit'—or to add its full title—'including the central connections, development and comparative anatomy of the visual apparatus'—was written originally in 1933. It rapidly became established as the standard work on the anatomy of the eye and its related structures with a world-wide circulation, and it is interesting that the author was an ophthalmic surgeon who built up a large and successful consulting practice in London. Apart from his hospital commitments, he was able to find time to make many original contributions in the fields of ocular anatomy and pathology and also in clinical ophthalmology, quite apart from the production of several textbooks.

The seventh edition of this treatise has been produced by Professor Roger Warwick, who is an anatomist of renown, and it is indeed fortunate that he has combined his interest in anatomy as a whole with a deep interest in certain aspects of ocular anatomy, particularly the complex distribution of the motor centres of the extrinsic ocular muscles in the brain stem. It is obvious that any book which has reached its seventh edition in just over 40 years must have increased in size and also altered in content, and though anatomy might be regarded as a fairly established subject it is interesting that about a quarter of the text has had to be rewritten since the previous edition was produced in 1968. It is interesting also, however, that many parts of the original text have been retained, with the beautiful illustrative drawings of the anatomical artist of renown, A. K. Maxwell. It seems perhaps a pity that there is no mention of the great contribution which was made by Professor R. J. Last in keeping the book alive with the production of the sixth edition after the untimely death of Eugene Wolff some years previously.

There can be very few criticisms of a book of this kind which has been written and maintained with scrupulous care over the years. It is a pity that the method of demonstrating the position of the eye in the orbit is limited to the injection of a saturated solution of lead nitrate into the eye, which is applicable only to the cadaver, whereas ultrasonography or the EMI scan can provide an accurate measurement in the living, as well as in the dead, state. There is no mention of Egger's line (the presumed circular line of attachment between the anterior vitreous face and the posterior lens capsule), which is perhaps a matter of anatomical debate, but it is of considerable importance in the management of congenital cataract, and clinical experience endorses the view that some form of tenuous attachment is a normal feature which becomes accentuated in certain pathological states. The description of the actions of the superior and inferior obliques is rather stereotyped and takes no account of the wide variations which the tendons of the superior oblique and the inferior oblique must make with the vertical meridian and which have a great clinical importance.

This book should be compulsory reading for any young person who is embarking on a career in ophthalmology, because a sound clinical knowledge must be built up on a firm background knowledge of the basic sciences. It should perhaps also be an essential item in the library of established ophthalmic surgeons.

KENNETH WYBAR

System of Ophthalmology, vol. XV, Summary of Systemic Ophthalmology and Indices. S. Duke-Elder and R. E. Soley. 1976. Pp. 490, refs. Henry Kimpton, London (£17·50)

Volume 15 of *System of Ophthalmology* is divided into three parts. Part 1 is a summary of systemic ophthalmology occupying 180 pages. It includes systemic, neurological, and dermatological diseases and syndromes with ophthalmological implications. References for each syndrome are given to the volume and page number of the *System*, and where important contributions have been made since the earlier volumes were published reference to these contributions has been appended. Part 2 is a small section giving an index of names of those who have contributed greatly to ophthalmology and whose biographies are illustrated elsewhere. The last

200 pages or so comprise the general index arranged by Miss Rosamund E. Soley. It adds to the usefulness of the *System*, making it possible to track down information which may be dispersed in several volumes. It also gives a bird's eye view of the 18 volumes which have preceded it, and although Sir Stewart has written 'The End' to his immense task it seems likely from his preface that he may make some plans to see that his great labour does not wither with time but is continued in some form into the future. STEPHEN MILLER

Adenine Arabinoside: An Antiviral Agent. By D. PAVAN-LANGSON, R. A. BUCHANAN, and C. A. ALFORD. 1975. Pp. 425, figs., tables, refs. North-Holland, Amsterdam ($25·95)

A symposium was held in San Francisco on 16–17 September 1974 to discuss the result of studies on antiviral activity of adenine arabinoside (ara-A). This book provides an authoritative summary of the information presented in that meeting.

The book is divided into 3 sections—preclinical, parenteral, and ophthalmic. The preclinical section presents papers describing the result of work on the antiviral activity of ara-A in cell cultures and in animals, and on the safety of the drug for parenteral and topical use. The parenteral section describes studies, still under way, to establish the effectiveness of ara-A in systemic and life-threatening viral infections. The ophthalmic section presents the results of extensive studies on the intraocular penetration of ara-A and of its efficacy against simple and complicated herpetic keratitis in comparison with idoxuridine and trifluorothymidine. The studies indicate that a new compound ara-A is as effective as IDU in treating herpetic keratitis, and gives evidence of the activity of this drug in a wide variety of other DNA virus-induced diseases.

This book is highly recommended to all ophthalmologists. S. DAROUGAR

Malignant Melanoma—Clinical and Histological Diagnosis. By VINCENT J. MCGOVERN. 1976. Pp. 178, 123 figs., tables, refs. John Wiley, New York (£16·00)

The author is clearly an expert in this particular field of pathology. His book is very readable and is profusely illustrated by both clinical and pathological photographs, but its title is somewhat misleading, because the author has included descriptions of benign melanotic tumours of the skin.

The book is composed of 12 chapters which deal in turn with pigmented naevi, their malignant potential, melanoma, spontaneous regression in these tumours, multiple primary cutaneous melanomata, their metastases, their prognostic features, their diagnosis by frozen section, the doubtful cases, the surgical approach, ocular melanoma, and problems concerning melanotic tumours in children. The problems of diagnosis of pigmented tumours are fully discussed.

There is an interesting account of Hutchinson's melanotic freckle, a lesion which may be difficult to differentiate from the well-known superficial spreading type of melanoma. The most important feature that distinguishes the two lesions is the presence of advanced solar degeneration of the skin in the former. Apart from the rare malignant blue naevus, the author recognises 3 main histogenetic patterns of development regardless of the presence or absence of a pre-existing naevus. He divides melanomas into 3 groups: invasive melanoma, with adjacent intraepidermal component of Hutchinson's melanotic freckle; invasive melanoma, with adjacent intraepidermal component of superficial spreading type; and invasive melanoma, without an intraepidermal component. The importance of recognising these 3 categories lies in the fact that each has a different prognosis, being worse when there is no evidence of an intraepithelial component. The author's classification is based on the work of Clark (1967), an international meeting of pathologists (1972), and on his own experience. In contrast to his classification of skin melanomata a recent meeting of pathologists at the World Health Organisation in Geneva reclassified tumours of the eye and its adnexa and divided melanomata of the skin of the eyelid into 4 recognisable histological types: melanoma arising in junctional or compound naevi, melanoma arising in blue naevi or cellular blue naevi, melanoma arising in intraepithelial melanosis, and melanoma of indeterminate nature.

The author has also discussed the relation between the prognosis of melanomata of the skin and the number of mitotic figures, the depth of tumour invasion, and the presence of a polypoidal structure. The prognosis is worse with increasing mitosis, depth of invasion, and when there is a polypoid pattern. On the other hand the presence of a continuous band of lymphocytes beneath the melanoma is usually an indication of spontaneous regression.

There is a short chapter on ocular melanomas, but it is impossible to cover this field adequately in a few pages. Some of the illustrations of choroidal melanomata are poor, and his assertion that the usual treatment of choice for conjunctival melanomata should be excision of the orbit will be severely criticised by ophthalmic surgeons who reserve this form of treatment for only a small percentage of cases, including those in which the melanoma has recurred and has invaded the orbit.

The author is to be congratulated on writing such an excellent treatise on melanotic tumours, and this book is highly recommended to all histopathologists. GWYN MORGAN

The Ophthalmic Assistant—Fundamentals and Clinical Practice. 3rd edn. Edited by H. A. SKIN and B. J. SLATT. 1976. Pp. 594, figs., tables. Mosby, St. Louis (London, Henry Kimpton) (£15·45)

The ophthalmic assistant, for whom this book is written, is the clinic or consulting room assistant who may have had no formal training but who needs a knowledge of anatomy, physiology, and optics as well as practical information on clinical methods, eye diseases, and medical and surgical treatment.

There are chapters on running the appointments office, spectacles, minor surgery, and hospital practice.

Three very informative chapters on contact lenses emphasise the growing importance of these in practice. Glaucoma, tonometry, tonography, and visual-field testing are described. There are an atlas of eye diseases, a glossary of terms, and tables of drugs. Practical advice on blind patients and their problems will be valuable to those meeting them for the first time. Backwardness in reading in children and the difficulties in the management of these disabilities are discussed fully.

The running of an eye clinic increasingly depends on ancillary staff, and this textbook provides for them a very useful guide. For those wanting to test themselves there is a list of questions after each chapter. G. B. COLLYER

The Visual Fields. A Text-book and Atlas of Clinical Perimetry. 4th edn. By D. O. HARRINGTON. 1976. Pp. 413, figs., refs. Mosby, St. Louis (London, Henry Kimpton) (£20·30)

In the introduction to the first edition the author quotes the old cliché that 'one picture is worth ten thousand words', and this led him to design the book as an atlas, a concept which is underscored by the retention of the word 'Atlas' in the title. As an excellently illustrated atlas Dr Harrington has undoubtedly achieved his objective.

In his preface to the fourth edition he points out that new complex instruments and techniques have lengthened the time requirements of perimetric examination, which has resulted in the delegation of much field examination to trained paramedical technicians. But he stresses that this should not relieve the ophthalmologist of the responsibility of carefully supervising such technicians and observing the response of the patient. 'When such an important subjective psychophysical test is not conducted by the physician it loses much of its diagnostic value' . . . and 'thus there is no real substitute for the visual field examination by the ophthalmologist himself'. This is a view that Traquair would certainly have endorsed.

The only criticism of this excellent atlas of clinical perimetry is that the reading as well as the distant visual acuity is not recorded on many of the charts. A superbly illustrated guide to the art of perimetry, this book well deserves the popularity it has achieved. G. I. SCOTT

Oculoplastic Surgery and Trauma. Edited by Pierre Guibor. 1976. Pp. 234, figs., tables, refs. Stratton Intercontinental, New York ($17·95)

This attractively presented volume contains the selected papers and round-table discussions of the annual meeting of the American Society of Contemporary Ophthalmology.

The first 4 chapters are devoted to the subject of ptosis, and the contents can be summarised in the words of one of the contributors, 'everyone who describes the anatomy of the levator seems to give a slightly different description . . .' There must surely be only one true description of anatomy, which regrettably does not appear in the chapters on the subject. Each contributor's approach to the surgery of ptosis is based on his own concept of the anatomy and pathology and does not clarify the existing confusion.

There follow several chapters on trauma of the orbital region, all of which are personal accounts of cases treated. It would have been better if the chapters on 'Epiphora following cosmetic surgery' and 'Complications of dacryocystorhinostomy' followed consecutively. There is a lesson for some in the former chapter although the 'retro-ovicular' and 'superclavicular' areas sounded strange.

The remaining presentations deal with lid tumours and their repair, entropion, the use of scleral grafts, fornix reconstruction, and the management of recurrent pterygia.

Without wishing to be unkind it must be said that unless illustrations speak for themselves they are better not included; the pity is that photography of poor quality detracts from an otherwise well produced volume.

The final round-table discussion makes interesting reading, particularly when dogmatism is challenged by reason. A. WERB

Vitamin A Deficiency and Xerophthalmia. WHO Technical Report Series No. 590. 1976. Pp. 88, figs. (4 in colour), tables. WHO, Geneva (Swfr8)

This valuable publication in paperback is the report of a joint WHO/USALD meeting, and would appear to cover all aspects of the problem. The introduction deals with definitions, significance, and prevalence. The second section covers the chemistry, sources, and metabolism of vitamin A, and this is followed by methods of assessment, ecology, a detailed account of prevalence, and treatment. Prevention is adequately covered. Valuable recommendations for research are added. There is a list of 86 references.

While this book would not have a great practical appeal to those practising in highly developed areas, it will be of inestimable value to those having to deal with the problem where it is rife. It is available at HM Stationery Office in London and many other cities in the United Kingdom. F. W. LAW

Correspondence

TO THE EDITOR, *British Journal of Ophthalmology*

Keeler award

SIR, It is now 10 years since the Keeler award for clinical study was founded by the generosity of Keeler Holdings Ltd, the parent company of C. Davis Keeler Ltd, and its then chairman and managing director, Mr Charles Keeler. The objects of the award were to enable British consultant ophthalmologists to travel to various parts of the world where new methods, techniques, and equipment were in use and to bring back first-hand information so that British ophthalmology might benefit. It was also envisaged that ophthalmologists from other countries might be enabled to visit Great Britain to demonstrate and speak about their particular expertise. A subsidiary purpose was to enable theatre sisters to visit other clinics in order to familiarise themselves with new equipment and methods. It was a condition of the foundation that the award's funds should be managed and disbursed entirely by the trustees, all of whom are ophthalmologists, and that the founders should take no part in the decisions, so that it could be seen that they had no commercial interest.

Up to the present time some 85 ophthalmologists and 9 nursing sisters have obtained awards totalling some £15 500. Many excellent reports have been received by the trustees and much of the knowledge brought back has been disseminated by papers read at scientific meetings or published in journals. There has been a tendency in recent years, particularly amongst registrars, for the awards to be considered as a means of further education for individuals visiting 'prestige' clinics abroad prior to applying for consultant appointments. This is not the true objective of the award. It is, however, justifiable for a senior registrar who is likely to take up, or be put in charge of, a particular subspecialty to be sent for extra training.

Elsewhere in this issue will be found the details and guidelines for those wishing to apply.

Yours sincerely,

E. C. ZORAB,
London W1 Chairman of Trustees

Notes

Keeler Award for Clinical Study

Those ophthalmologists wishing to apply for an award in order to study some particular aspect of ophthalmology with a view to bringing to this country new ideas and methods from overseas should in the first instance write to: The Secretary, Keeler Award, Angus, Campbell & Co, Metropolis House, 39–45 Tottenham Court Road, London W1P 0JL. They will then be sent an application form and details of the full purpose of the award. They will also receive the trustees' conditions and advice.

International Society of Geographical Ophthalmology

The meeting arranged in Tunisia in May 1977 has been cancelled, but a meeting will be held in Cagliari, Sardinia, during 25 to 29 September 1977. There will be symposia on the geographical distribution of ocular viral diseases and congenital disorders. Free papers concerned with geographical ophthalmology will also be presented. Further details from Dr E. E. Cass, Box 688, Fort Smith, N.W.T., XOE 0PO, Canada.

Impaired Vision in Childhood

Jerusalem, 8 to 13 May

The main topics to be discussed are: (1) epidemiology of impaired vision in childhood; (2) cataract in infancy; (3) metabolic and genetic diseases; (4) congenital anomalies; (5) amblyopia: concepts, prevention, and treatment; (6) vitreous retinal vascular diseases including RLF; (7) congenital glaucoma; (8) tumours in infancy; (9) tapeto-retinal degenerations; (10) trauma in infancy and childhood, prevention and treatment; (11) refractive errors in infancy; (12) rehabilitation of low vision and blindness in childhood; (13) inflammatory diseases and other subjects. The Ticho memorial lecture will be delivered by G. von Noorden during the congress on the subject 'New Research Aspects and their Application on the Prevention and Treatment of Amblyopia'. Further information on writing to the Congress Secretariat, POB 983, Jerusalem, Israel.

Symposium on Vitreous Surgery

Windsor, 28 May

A symposium on vitreous surgery will be held at the Postgraduate Medical Centre, King Edward VII Hospital, Windsor. It will encompass both anterior and posterior segment surgical techniques, including selection and care of instruments, indications, patient evaluation, complications, and results. Enrolment is limited and advanced registration is required. For further details write to J. J. Kanski, FRCS, King Edward VII Hospital, Windsor, Berks.

Symposium on Metabolic Eye Disease

Kyoto, Japan, 20–22 May 1978

The third symposium of the International Society on Metabolic Eye Disease will be held in Kyoto, Japan, 20–22 May 1978, after the international congress of ophthalmology. Papers are invited on advances in enzymology in metabolic eye diseases as they affect cataract, retinopathy, corneal dystrophy, carbohydrate metabolic defects, mucopolysaccharidosis, and lipoprotein and amino-acid disorders. They should be sent to Heskel M. Haddad, MD, Program Chairman, 1200 Fifth Avenue, New York, New York 10029. Abstract deadline 1 November 1977. Membership dues $20 annually: registration fees $30 (members), $60 (non-members).

International Society for Cornea Research

Kyoto, Japan, 12 and 13 May 1978

Two-day meetings with symposia, round-table discussions, and free papers. Topics for the meeting are: corneal immunology: inflammation, infection, and transplantation. Clinically relevant studies on the endothelium and epithelium. Registration is limited to 100. Direct abstracts of free papers to: Stuart I. Brown, MD, Eye and Ear Hospital, 230 Lothrop Street, Pittsburgh, Pennsylvania 15213, USA.

Third International Symposium on Orbital Disorders

Amsterdam, 5–7 September

This symposium will be devoted to basic, diagnostic, and therapeutic approaches to orbital disorders including inflammation, neoplasm, vascular anomaly, endocrine disturbance, congenital deformity, and trauma. Further details from Dr J. P. A. Gillissen, secretary general, c/o University Eye Hospital, Wilhelmina Gasthuis, Eerste Helmersstraat 104, Amsterdam-1013, The Netherlands.

Edridge-Green Lecture

The Edridge-Green Lecture entitled 'The retinal pigment epithelial interface' will be delivered under the auspices of the Royal College of Surgeons of England by Professor W. S. Foulds, FRCS, on Thursday, 9 June, at 3 p.m. at the Institute of Ophthalmology, Cayton Street (adjacent to Moorfields Hospital, City Road), London. Tickets will not be required.

James Joyce's Eyes

The Royal College of Physicians of London has put on an exhibition entitled 'My Impossible Health', with a subtitle 'The Case of James Joyce'. It sketches with the resources of the college library the medical history and associations of one of the foremost writers of the first half of the 20th century. Much of Joyce's impossible health was due to iritis and its consequences, and therefore this exhibition holds a particular interest for ophthalmologists. It consists largely of pictures and photographs with captions explaining the association of the photograph with Joyce's life, and anyone who has a spare hour can fruitfully employ it in a visit to this fascinating display of the many aspects of Joyce's character.

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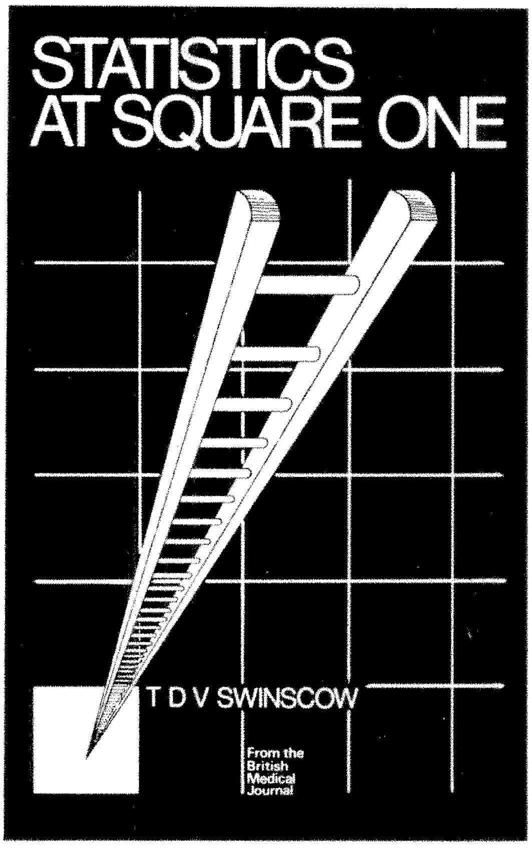

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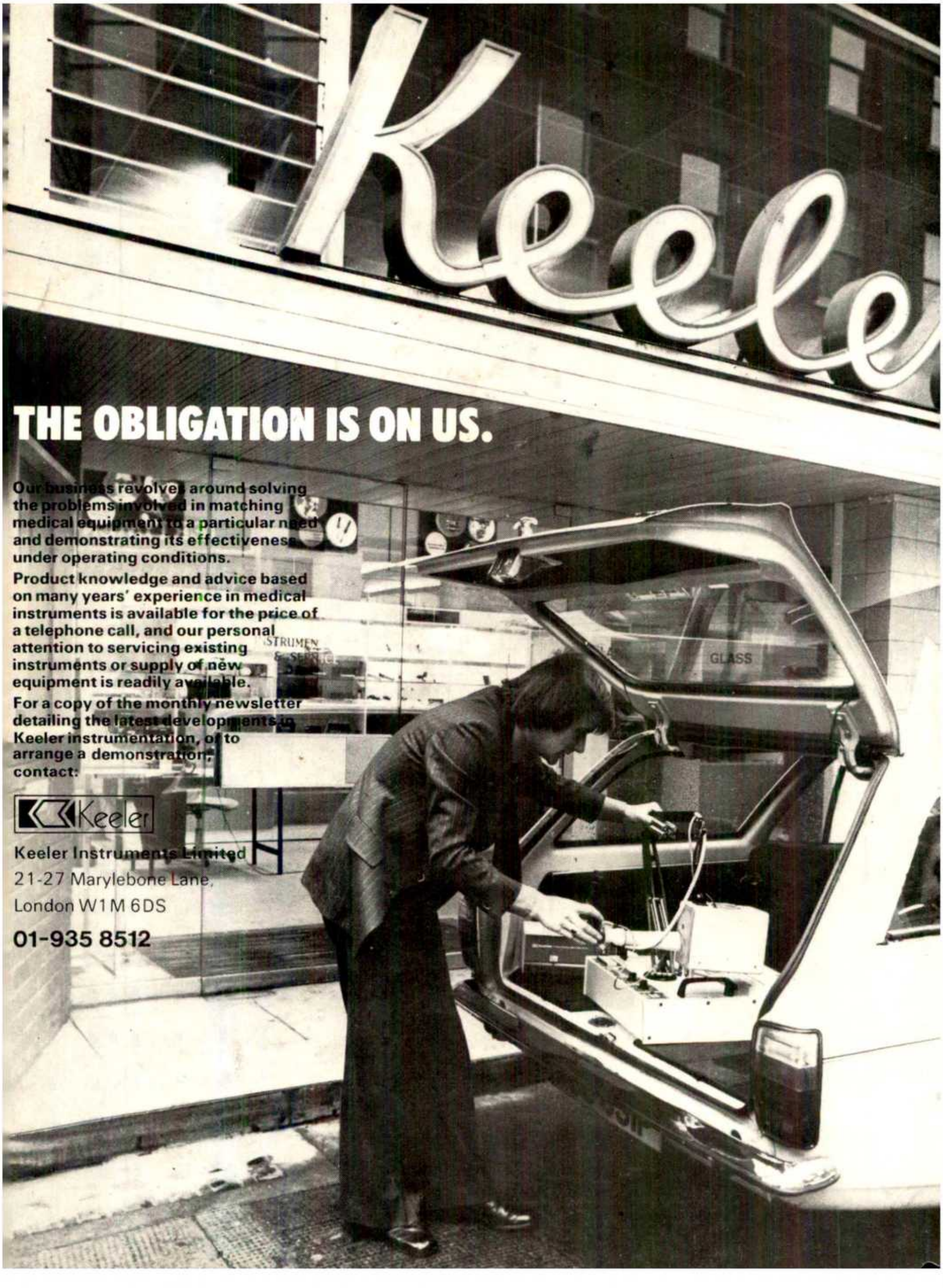

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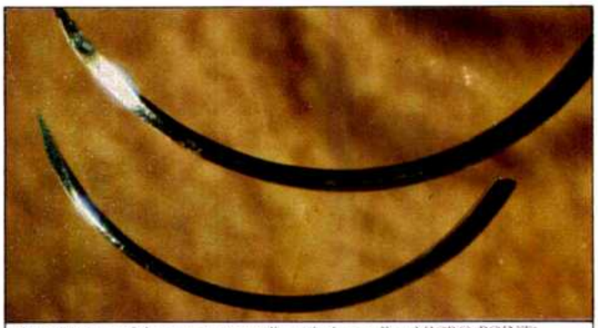
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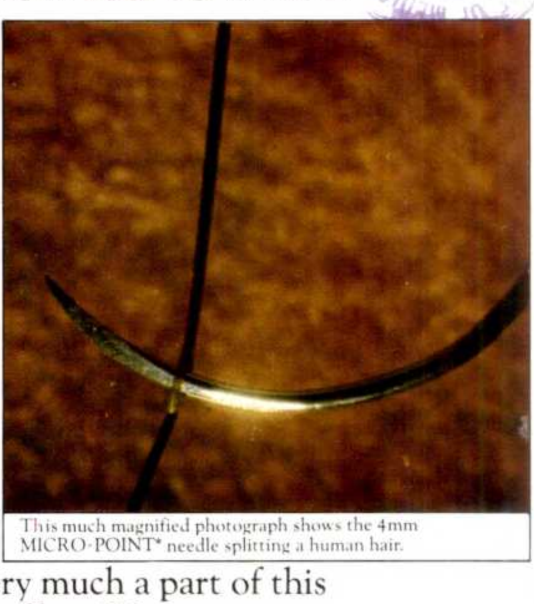
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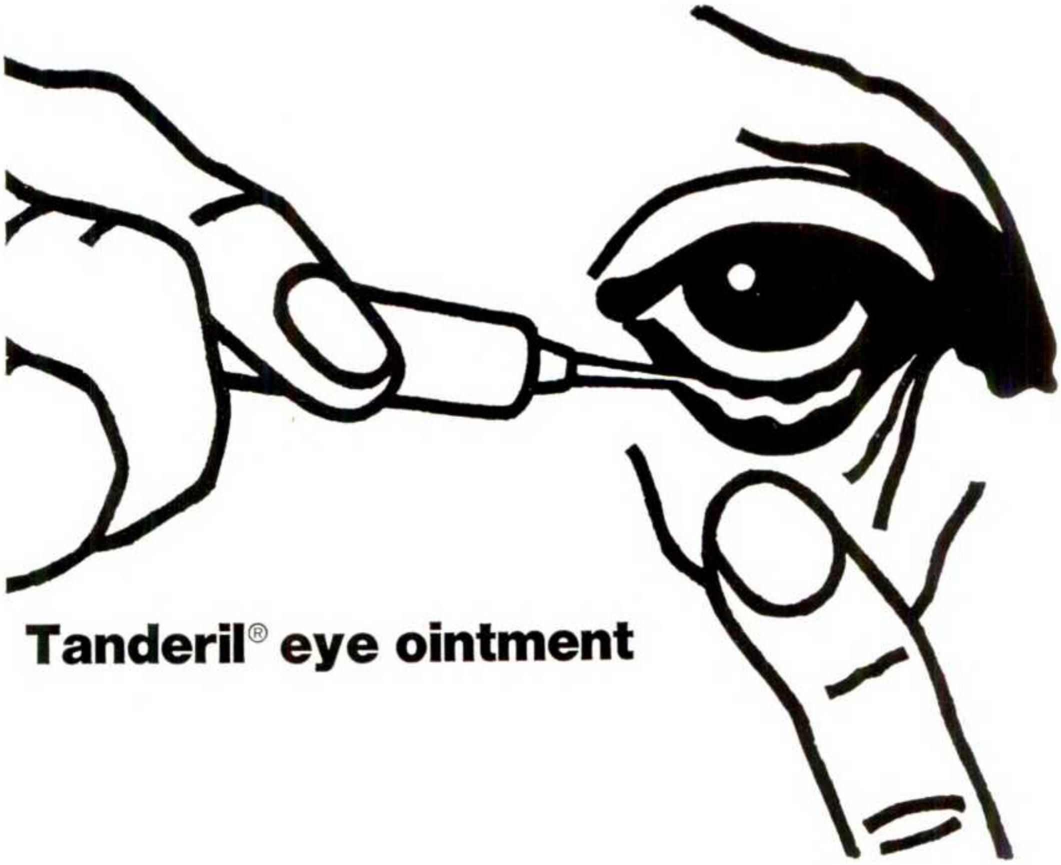

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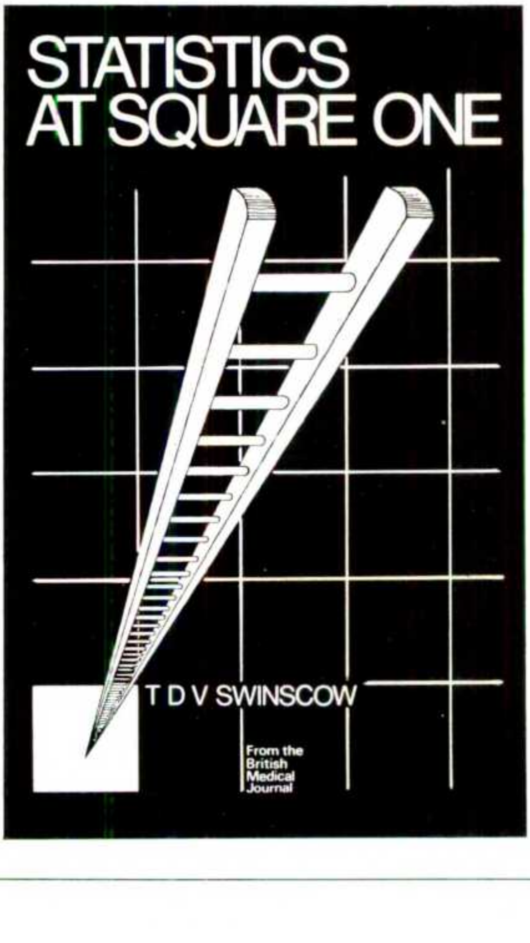

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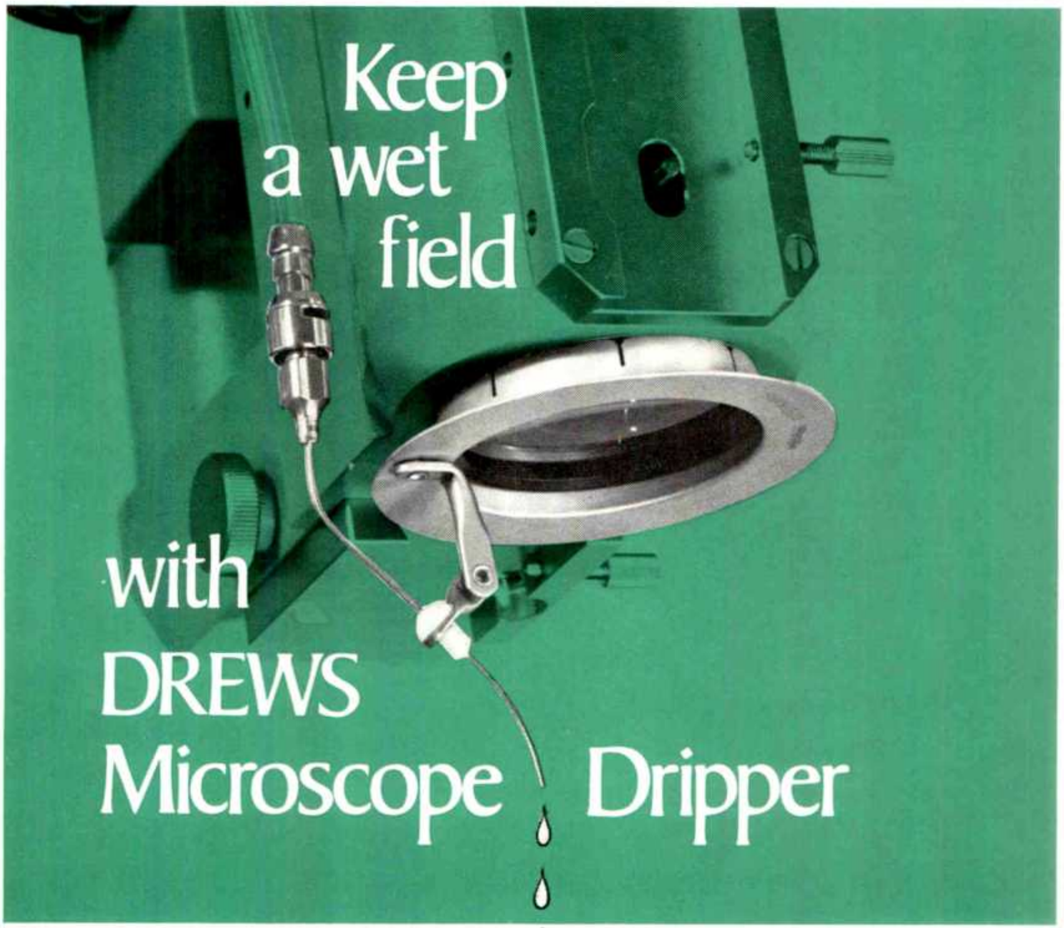

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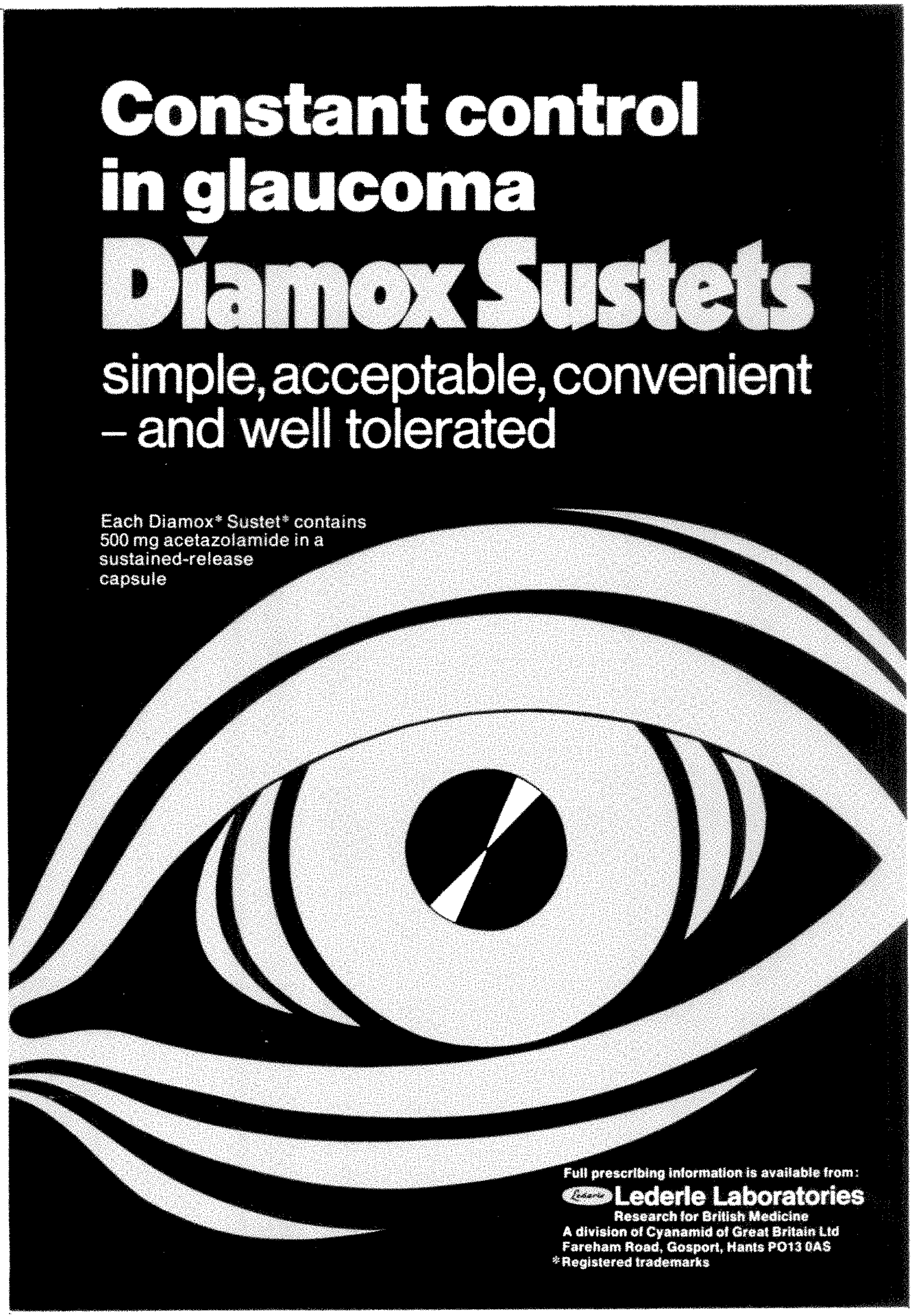

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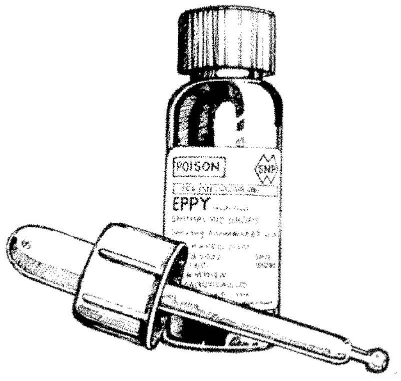

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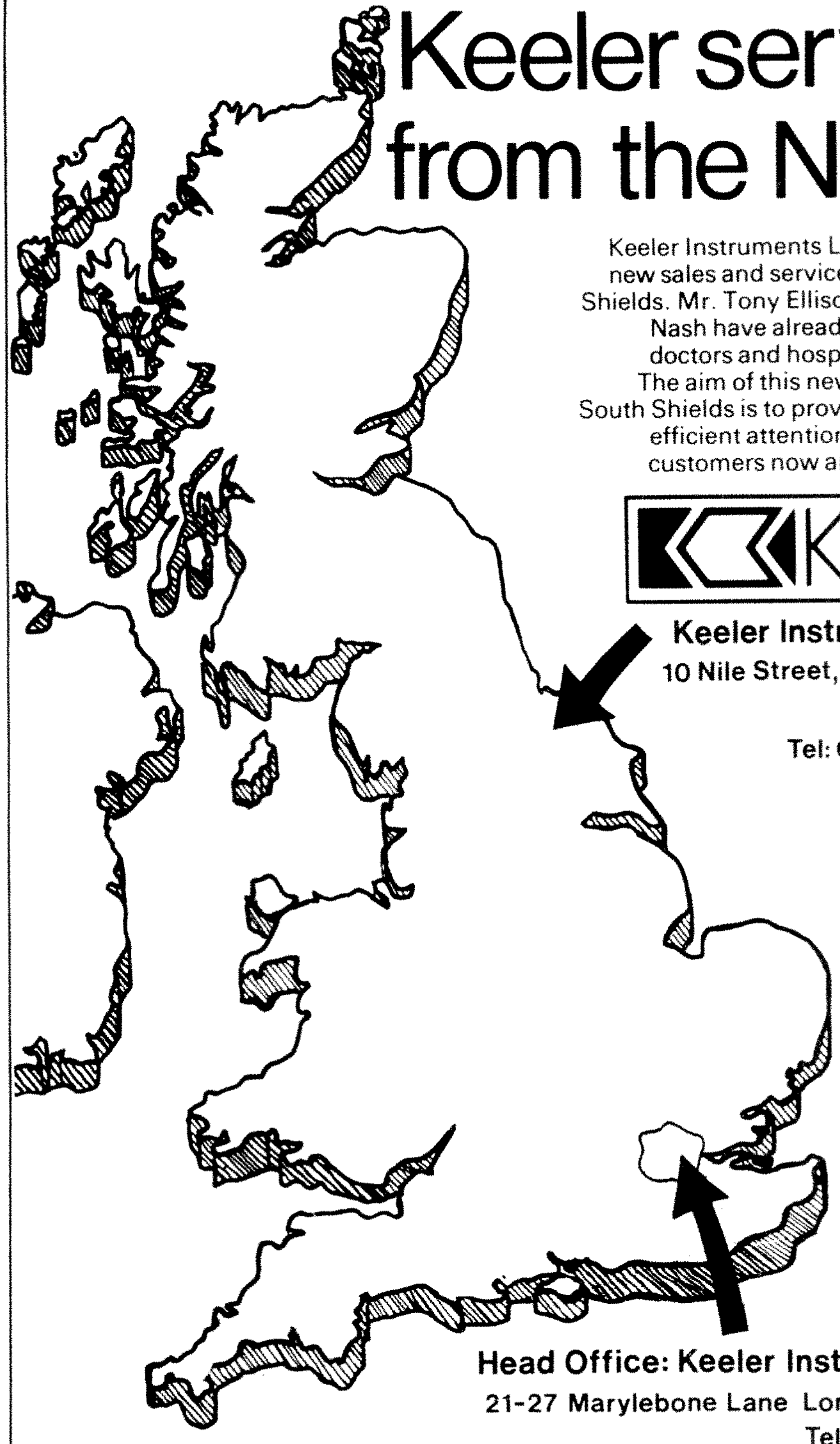

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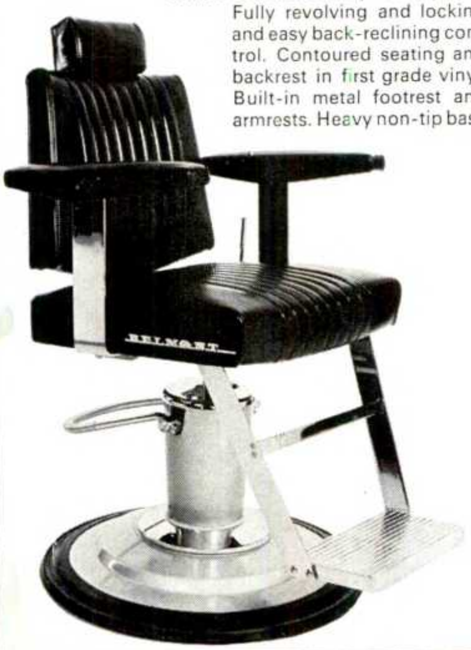

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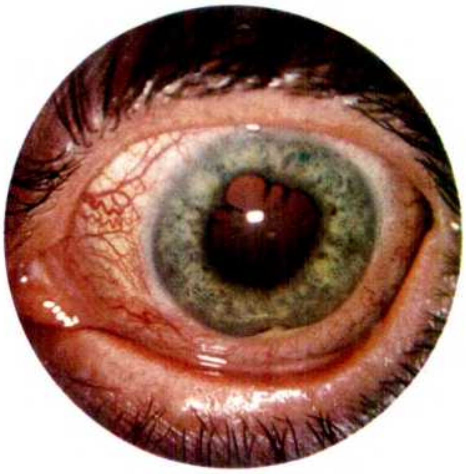

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British Journal of Ophthalmology, 1977, **61**, 307–309

Editorial: Current status of intraocular lenses

The past 5 years have seen a reawakening of interest in intraocular lenses after the early disasters of the mainly angle-fixated lenses. The subject has been kept alive owing to the work of Choyce in England and Binkhorst in Holland, and it can now be conservatively estimated that there have been 50 000 American and 10 000 European intraocular implant operations. Implant societies are being formed in many parts of the world. Recently the United Kingdom Intraocular Implant Society was formed, with Mr Neil Dallas as its first president (see p. 000).

The well-known advantages of intraocular lens implantation are: Freedom from patient handling, minimum aniseikonia, rapid return of binocularity, and normal peripheral vision. However, the operation is undoubtedly technically difficult, and such complications as corneal dystrophy, implant dislocation, pupil block glaucoma, and cystoid maculopathy have led to a conservative approach by many surgeons.

All intraocular lenses should be made of monomer-free polymethylmethacrylate (PMMA), as was used by Ridley for his first posterior chamber implant in 1949. PMMA has been shown in 30 years of clinical use to be remarkably free from degradation *in vivo*. At present there are 4 European manufacturers of lathe-turned lenses, while the 8 American firms generally produce moulded lenses. Lenses are biconvex or plano/convex, 4 to 6 mm in diameter. Most firms supply lens powers from 10 to 25 dioptres in aqueous. The standard-power lens of 19·50 dioptres in aqueous is approximately equivalent to an 11·0-dioptre sphere spectacle lens; this usually produces iseikonia. Individual lens power can be assessed in an aphakic eye for secondary implantation by refraction. However, lens-power measurements for primary implantation necessitate axial length measurement with ultrasonography, keratometry, and the use of standard calculation tables as produced by Binkhorst and others. Generally speaking, the standard 19·50-dioptre lens is used except in children, who require a more powerful 22·50-dioptre lens. Supporting lens loops are either made from polyamide (nylon), which, while being light and easily manufactured, may be a potential source of weakness, as it is hygroscopic (though nylon has been shown not to be attacked by pure water), or polypropylene (Prolene), which is probably more stable, being less hygroscopic and already available. Metal loops of platinum/iridium, titanium, and gold alloy are said to be inert, though few *in vivo* data are available. They are heavier than plastic, with a greater tendency to iris sphincter erosion; moreover, anterior dislocation produces greater corneal endothelial damage.

Iris suture materials in use are 22 to 24 μm polyamide (Perlon or Ethilon), which, being hygroscopic, may disintegrate in time. More stable polypropylene, platinum/iridium, or stainless steel wire is available swaged to 5 to 6 mm iris needles.

Sterilisation of implants

Dry or moist heat sterilisation gives plastic degradation to harmful monomers, while excessive irradiation makes PMMA brown and brittle and should be avoided. Considerable satisfactory clinical experience of the caustic soda method of F. Ridley has made it the sterilisation method of choice since 1957. Objections have been made to chemical sterilisation by some authorities recently, and its effectivity against fungi has been challenged.

Types of cataract surgery suitable for intraocular lenses

Implant surgery should be performed with the aid of the operating microscope to ensure watertight closure of the wound. Postoperative flat anterior chamber with plastic-endothelial contact can give rise to corneal endothelial decompensation. Cases to avoid include uncontrolled glaucoma, overt corneal dystrophy, younger diabetics, retinal detachment (history of either eye), and uniocular patients.

Primary implantation after intracapsular extraction provides a rapid return of visual function, but may have a higher late incidence of cystoid macular oedema.

Binkhorst has revived interest in planned extracapsular surgery, claiming that capsular fixation of his 2-loop lens gives a deeper anterior chamber, normal pupillary function, less prosthesis movement (pseudophakodonesis), and a lower incidence of endothelial corneal dystrophy, cystoid maculopathy, and retinal detachment. The disadvantages are: sometimes a slower return of visual function owing to cortical remnants and the necessity of up to 30% subsequent capsulotomies.

Secondary insertion of an intraocular lens after contact lens failure is particularly rewarding. Nevertheless, an eye with vitreous knuckle or free vitreous in the anterior chamber should be approached with great caution.

Intraocular lenses in current use

ANTERIOR CHAMBER FIXATED LENSES

Choyce Mark VIII (Fig. 1*a*) fabricated of PMMA only with a 6-mm optic (4-mm optic if coloured haptic); available in various lens powers. Weight is 25 mg in air. The haptic feet lie on the iris root behind the scleral spur. Implant size is calculated by measuring either the horizontal or vertical corneal diameter and adding 1·00 to 1·50 mm. It can be used either as a primary or secondary implant, being reasonably simple to insert and giving normal pupillary function without fear of dislocation. It is especially useful in the presence of large iris colobomata. However, several peripheral iridectomies are required to avoid pupil block glaucoma. This lens, therefore, should not be used in eyes with prior angle PAS or shallow anterior chambers.

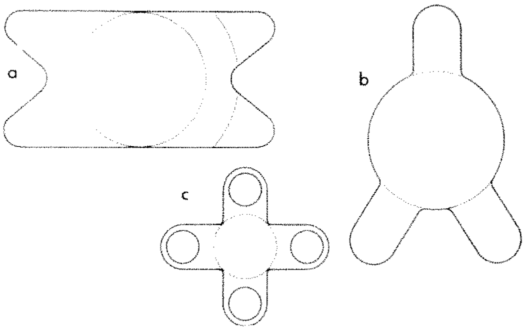

Fig. 1 a *Choyce lens (Mark VIII)*. b *Ridley's tripod lens*. c *Epstein-Copeland Maltese lens*

The Ridley tripod anterior chamber lens (Fig. 1*b*) is similarly placed as the Choyce Mark VIII in the anterior chamber, but this lens has few followers.

IRIS PLANE LENS

Epstein-Copeland Maltese cross plane lens (Fig. 1*c*) 4-mm optic of PMMA; weight 7·5 mg in air. Two limbs lying anterior and 2 posterior to the iris sphincter. This lens has little following outside the United States. It is simple to insert, but miotics are generally necessary. It is especially prone to pupil block glaucoma, chronic iritis, and formation of pupillary membrane. It is also said to be associated with a higher incidence of cystoid maculopathy.

BINKHORST (FIG. 2*d*) AND FEDEROV (FIG. 2*e*) 4-LOOP IRIS SUPPORTED LENSES

In use since 1958. 5-mm optic, weight 14 mg in air, with 2 anterior and 2 posterior loops of polyamide, angled backwards. Available in various lens powers. The Federov lens has the posterior loops at right-angles to the anterior loops (said to have a lower incidence of implant dislocation).

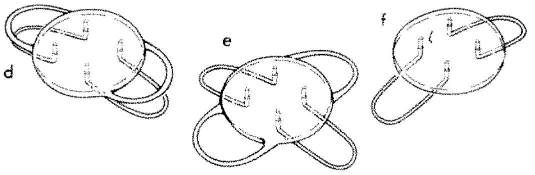

Fig. 2 d *Binkhorst 4-loop, iris-clip lens*. e *Federov iris-supported lens*. f *Binkhorst 2-loop lens*

These lenses can be used after intra- or extracapsular surgery and are simple to insert. The loops can be sutured together through a peripheral iridectomy or directly sutured to the iris. Without suture fixation of the implant the patient may have to be kept on miotics, and iris sphincter atrophy may occur.

Adequate peripheral iridectomies are essential to avoid pupil block glaucoma. Vertical meridian implantation of the Binkhorst lens should be performed to avoid any possibility of endothelial contact from the anterior loops in horizontal eye movements.

The Binkhorst 3-loop lens is without 1 anterior loop and is used in association with iris suture fixation of the remaining anterior superior loop.

BINKHORST 2-LOOP IRIDOCAPSULAR LENS (FIG. 2*f*)

In use since 1965. 5-mm lens available in various powers; 2 posterior loops of either polyamide or metal; weight with nylon loops is 12 mg in air. The posterior loops are theoretically placed in the capsular bag to give capsular fixation without implant movement, thereby allowing normal pupillary function. Other advantages claimed by Binkhorst of extracapsular surgery associated with an iridocapsular lens have been enumerated in a previous paragraph.

WORST MEDALLION LENS (FIG. 3*g*)

In use since 1969. A 5-mm optic PMMA available in various lens powers from 10·00 to 21·75 dioptres

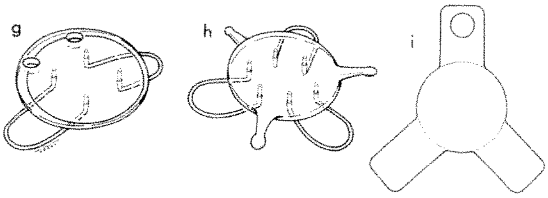

Fig. 3 g *Worst Medallion lens*. h *Federov Sputnic lens*. i *Little-Arnott posterior chamber lens (Mark I)* in aqueous. Each lens has a 1-mm fenestrated haptic of PMMA, the posterior loops being of nylon or titanium. Some of these lenses allow for a very small pupil (as small as 1·2 mm). Iris fixation is either by direct suture through a fenestration in the haptic or by Worst's transiridectomy safety-pin fixation; the posterior wire loop is pinned over an anterior safety clip through a peripheral iridectomy. Various models are available, suitable for intra- or extracapsular extraction.

FEDEROV SPUTNIC LENS (FIG. 3*h*)

This is similar in principle to the Binkhorst 4-loop lens, having 3 posterior loops and 3 anterior prongs of polyamide attached to the optic (or moulded to the optic) lying in front of the iris.

KRASNOV EXTRAPUPILLARY LENS

The first model has a 5-mm optic with 2 prongs of gold alloy which are placed through the irido/puncture; the second design has 1 prong looped for placing a direct iris suture. It is claimed that this lens design allows normal pupillary function (see p. 000).

Posterior chamber lenses

PEARCE TRIPOD AND BIPOD POSTERIOR CHAMBER LENS

A 4-mm optic with 3 or 2 limbs at varying radii, fabricated of PMMA. The tripod lens weighs 9 mg and the bipod 8 mg in air. This lens is used after extracapsular extraction with or without direct iris suture fixation through a limb fenestration. Standard power lens is 21·0 D in aqueous; other powers will be available. It is claimed that this lens allows normal pupillary function, no possibility of endothelial contact with little danger of pupillary-block glaucoma (peripheral iridectomies can be omitted) (see p. 000). Aniseikonia is reduced to the minimum, the lens being in the corrected anatomical position in the eye. However, lens centration outside the visual axis and subsequent capsulotomies are postoperative complications.

LITTLE-ARNOTT POSTERIOR CHAMBER LENS (FIG. 3*i*)

A 5-mm optic with a tripod configuration.

Lens dislocation is the only complication peculiar to implant cataract surgery. Discussion of other aphakic complications, such as endothelial corneal dystrophy, cystoid maculopathy, sepsis, and retinal detachment, is concerned with their incidence with and without lens implantation.

Implant surgery has stimulated considerable research into safe intraocular plastics, iris suturing materials, aphakic cystoid maculopathy, and retinal detachments. Recently it has revived, in conjunction with phako-emulsification techniques, a fresh assessment of the value of extracapsular cataract surgery.

A conservative approach to intraocular implantation would be to select suitable cases over the age of 65, implanting in 1 eye only, and avoiding monocular patients. At present a safe plastic in PMMA is in use, which has passed 20 years of extensive clinical testing. Patients with successful intraocular lenses are generally satisfied. However, development of a safe permanent-wear soft contact lens, not requiring constant supervision by the patient and giving the same optical qualities as an intraocular lens, may make implantation an unnecessary risk.

British Journal of Ophthalmology, 1977, **61**, 310–315

Sixteen months' experience with 140 posterior chamber intraocular lens implants

JOHN L. PEARCE

SUMMARY Three main designs of posterior chamber lenses in 140 cases have been reviewed. The visual results are satisfactory; patient satisfaction is good; and postoperative complications are limited to anterior dislocation of the feet of the lens and the necessity to wash out cortical remnants from behind the prosthesis in a small percentage of cases. The posterior chamber prosthesis is free from some of the complications of other intraocular lenses and probably provides the most 'normal' looking eye of any pseudophakoi.

The author has reported (Pearce, 1976) a small series of patients in whose eyes lightweight posterior chamber intraocular lenses were implanted. This paper considers further experience in 140 cases with modifications in lens design and in surgical technique.

In America cataract surgery by the extracapsular technique has recently been favoured, particularly since the advent of phaco-emulsifying and aspiration irrigation techniques, which facilitate the complete removal of cortical remnants. The equipment, however, is expensive and is likely to be available in only a limited number of European centres.

The pathogenesis of aphakic cystoid macular oedema is still speculative, although two types have been recognised. The Irvine-Gass syndrome of transient macular oedema occurs in up to 40% of cataract extractions, and the Jaffe syndrome of definite cystoid macular changes without oedema, wherein recovery of visual function is often limited, occurs less frequently. The incidence of cystoid macular oedema in pseudophakia is variously reported as being between 5 and 12%, with a higher incidence after intracapsular cataract extraction. Binkhorst *et al.* (1976) stated that their series showed a definite superiority of extra- over intracapsular cataract surgery so far as the long-term protection of the retina was concerned, with special reference to cystoid maculopathy and retinal detachment. Capsular fixation, as contrasted with iris support lenses, has an increasing number of advocates, though capsular fixation is not always successfully attainable. Inert iris suture materials such as polypropylene and platinum-iridium wire avoid the disintegration of iris sutures with time.

It seems likely that in future a balanced salt solution incorporating gluthathione and adenosine will become available for anterior chamber irrigation, because it reduces postoperative corneal oedema and the risk of endothelial damage.

Current design of Pearce bipod and tripod posterior chamber lens

Different lengths of the fenestrated haptic feet are available, otherwise the basic design of the lens (Fig. 1, Table 1) is unchanged, being fabricated of polymethylmethacrylate (PMMA) with a 4-mm optic of lens power equivalent to a spectacle lens of +11·50 D at a vertex distance of 10 mm or a thin lens of 21·0 D in aqueous. Shortly, lenses of 19 and 23 dioptre in aqueous will be available; the weight of the lens remains between 8 and 9 mg in air.

The bipod lens is generally used for secondary insertion through a small incision after prior extracapsular extraction. It can also be used combined with penetrating keratoplasty, being sutured by a double Pearce iris stitch.

The tripod lens is normally inserted in an inverted 'Y' fashion with the superior limb directly sutured through the fenestration to the iris. Choice of length of inferior limbs depends on the pupil size after extracapsular extraction is completed. If the pupil remains large, it is wise to insert a lens with 5 mm radial inferior feet, otherwise anterior dislocation of the inferior limbs may occur postoperatively. A tripod lens is now available with 4·75 mm radial limbs, which can be used without iris fixation

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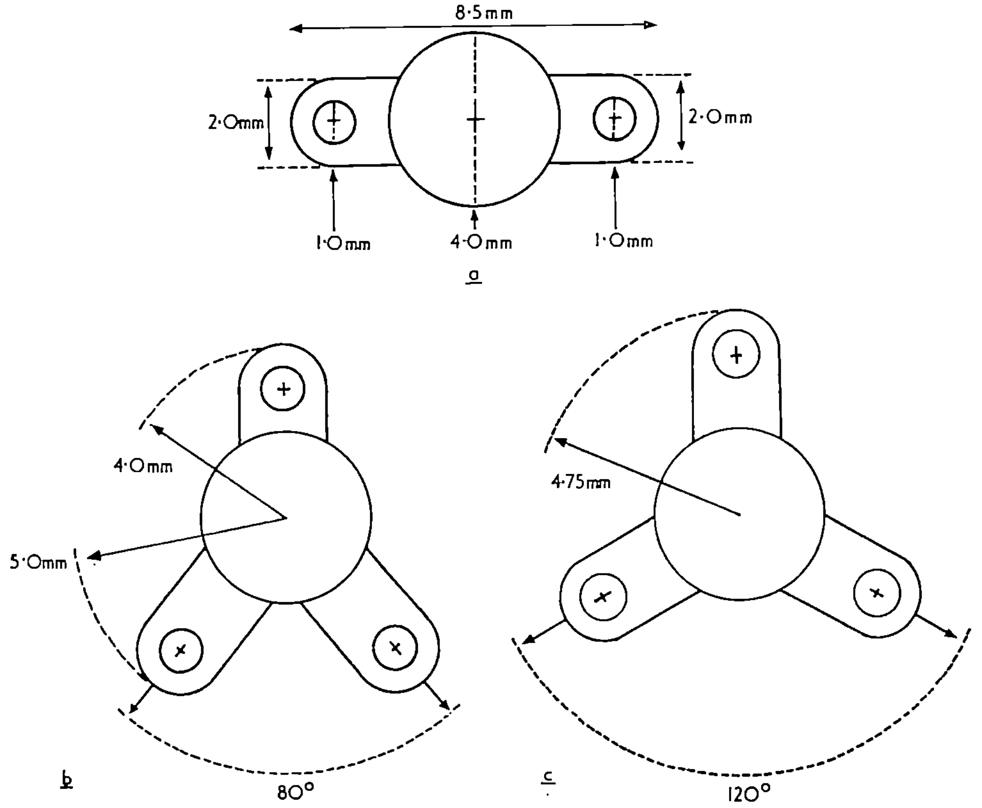

Fig. 1

Table 1 *Design of lenses*

Type	*Form*	*Angular separation Inferior limbs*	*Superior limbs*	*Inferior limbs*
			(mm)	*(mm)*
493A	Bipod	—	4·25	4·25
493B	Tripod	80°	4·00	4·50
493C	Tripod	80°	4·00	5·00
493D	Tripod	120°C	4·75	4·75
493E	Tripod	80°	4·75	4·75

All limbs 0·25 mm thick, 2·0 mm wide; fenestration 1·0 mm.
Standard optic diameter 4·00 mm equiconvex.
Standard powers: In aqueous +21·50D equivalent spectacle correction +12·00.
Other powers: In aqueous +19·00D equivalent spectacle correction +11·00; in aqueous +23·00D equivalent spectacle correction +13·00.

provided adequate anterior capsule is left below to allow capsular fixation.

Surgical technique

All surgery is performed under the operating microscope with continuous irrigation of the cornea with Ringer's solution.

PREOPERATIVE TREATMENT

Maximum mydriasis is obtained by topical instillation of cyclopentolate 1% with phenylephrine 10%.

OPERATION

- *(a)* A scissor incision is made of a small limbal-based conjunctival flap.
- *(b)* A 9-mm, two-thirds thickness perpendicular (100 degrees) groove is incised with a diamond knife 1 mm from the surgical limbus.
- *(c)* Three 10/0 Perlon corneal stitches are pre-placed in the gutter and looped out of the wound.
- *(d)* The anterior chamber is entered with a small incision by the diamond knife.
- *(e)* A hooked-over 22-gauge hypodermic needle attached to a 5-ml syringe filled with Ringer's solution is used as a cystitome. Multiple closely placed rotary tears around the anterior capsule about 1 mm from the equator of the lens are performed. This is the 'beer can' technique of anterior capsulotomy.
- *(f)* The eye is then opened with the diamond knife and the anterior capsule removed with Arruga's intracapsular forceps.

(g) The nucleus is dislocated into the anterior chamber using a lachrymal cannula attached to a syringe filled with Ringer's solution. The tip of the cannula can be passed partly underneath the nucleus, so that the nucleus is partly washed into the anterior chamber.

(h) A small vectis is passed underneath the nucleus and the nucleus lifted out of the anterior chamber. The remaining cortical fragments are washed out, it being wise to avoid aspiration unless the depth of the anterior chamber is maintained. Even with a slit-lamp beam it may be difficult to distinguish between a thin clear layer of posterior subcapsular cortical material and the posterior capsule itself. With experience this layer can be peeled off, using an irrigating cannula or a cannula with a sand-blasted tip.

(i) *Pearce iris stitch.* The iris sphincter is gripped with the suture-tying forceps at 12 o'clock. 5-mm corneoscleral needle swaged to polyamide, polypropylene, or platinum/iridium wire is passed through the pupil behind the iris. The point of the needle emerges at 12 o'clock some 2 mm from the limbus (when about half the chord length of the needle is covered by iris) and is then laid aside. The loose ends of the iris stitch are placed through the fenestration of the haptic foot of the lens and tied, the free ends being excised.

(j) The anterior chamber is filled with air and the lens is placed within the capsular bag using the special introducing forceps (air within the anterior chamber facilitates the identification of the anterior capsule remnants and also acts as a buffer between the prosthesis and the corneal endothelium).

(k) The iris at 12 o'clock is placed over the superior limb of the prosthesis, and another bite of the iris is taken circumferentially just behind or in front of where the stitch emerges from behind the iris, leaving a small loop; this is tied and the ends are cut with curved Vannas scissors.

(l) Provided adequate anterior capsulectomy and removal of cortex has been performed there seems to be little need for a peripheral iridectomy. Corneoscleral sutures are tied, air is removed from the anterior chamber, and this is refilled with Ringer's solution, the lens being centred in the optical axis with an air cannula. The conjunctival flap is closed.

(m) Subconjunctival depot steroid with an antibiotic is injected into the lower fornix; eyelids are closed after removal of the plastic drape, and a pad and cartella are placed over the eye.

POSTOPERATIVE TREATMENT

The first dressing is performed the following morning, the patient being allowed up as soon as the effect of the anaesthetic has worn off. Topical steroids and short-acting mydriatic/cycloplegic drops such as cyclopentolate are instilled for 2 to 3 weeks to keep the pupil active. The return of visual function is rapid provided there is no lens matter behind the implant.

Operative complications

Vitreous loss. Expression of the nucleus was followed by vitreous loss in 2 of the earlier cases with Binkhorst posterior chamber lenses.

Case 1. Present visual acuity is 6/6 unaided. The patient developing cystoid maculopathy which resolved after a course of indomethacin.

Case 2. Present visual acuity 6/18 15 months after surgery. This case has a dry senile macular degeneration.

There have been no other serious operative complications. However, removal of all cortical remnants, especially in an immature cataract, can be time-consuming, it being important to use a microscope with coaxial illumination perpendicular to the cornea.

EARLY POSTOPERATIVE COMPLICATIONS

Implant dislocation. Anterior dislocation of 1 or 2 of the inferior feet of the implant has been noted in 4 eyes (3%) within 2 days of surgery. This may have been due to immediate excessive postoperative pupillary dilatation, and it has not been possible to reposition any of these lenses medically. All have been repositioned surgically under local anaesthetic through a small stab incision in the cornea without retrobulbar anaesthesia. Posterior dislocation of the lens has been absent in this series.

Striate keratitis has become increasingly less noticeable with improvement in extracapsular technique, avoidance of aspiration of cortical remnants, and reduction of the size of the corneoscleral wound from 170 to 100 degrees.

Surgical uveitis has been minimal, with no case of hypopyon or hyphaema. The absence of a peripheral iridectomy possibly contributed to the lack of haemorrhage.

LATE POSTOPERATIVE COMPLICATIONS

Bullous keratopathy. One case has bullous keratopathy of the upper third of the cornea. The patient wears a soft contact lens and has a corrected vision of 6/9 6 months after surgery. In addition there is one further case of corneal oedema in an eye with traumatic cataract, but the oedema is gradually subsiding.

Decentred lenses. Nine eyes (6%) were found to have the lens too far from the visual axis and required centration by means of a McCannel iris stitch.

McCannel iris stitch technique

(a) Local anaesthesia is given, with facial nerve akinesia.

(b) A diamond knife is used to cut a 2-mm corneal incision 2 mm from the limbus adjacent to the theoretical position of the implant.

(c) A 5-mm iris needle swaged to polypropylene, polyamide, or platinum/iridium wire is passed through the incision, and through and behind the iris and inferior foot of the lens, the point of the needle passing through the fenestration in the lens foot, which can be seen silhouetted against the iris, then out through the iris and cornea by counter-puncturing.

(d) A hooked hypodermic needle attached to a syringe filled with Ringer's solution is passed through the original incision. The suture within the anterior chamber is picked up by the needle hook and pulled back out of the eye.

(e) The suture is tied, the ends cut flush with the knot, and the anterior chamber reformed with balanced salt solution.

Capsulotomies. Condensation and fibrosis of the posterior capsule have been rare in this short follow-up. However, 12 eyes (8·5%) have required or will require irrigation of cortical remnants which were behind the prosthesis. Generally this can be performed under local anaesthesia through a small corneal stab incision, washing out the cortical remnants from behind the posterior capsule. The posterior capsule can be polished using a sand-blasted cannula.

Results

There were 140 eyes with a follow-up from 1 week to 17 months. The average time since surgery was 6·5 months. The average age of the patient was 69 years, with a range from 2 to 93 years.

The designs of lens used comprised 18 Binkhorst posterior chamber lenses (Binkhorst 4-loop lens with the posterior loops excised), 18 Pearce bipod lenses, and 104 Pearce tripod lenses. Two patients had combined keratoplasty and posterior chamber lens insertion of the bipod design, and an additional patient with prior penetrating keratoplasty for conical cornea. Sixty-nine eyes had 2 peripheral iridectomies, and in 71 eyes the peripheral iridectomy was omitted.

VISUAL RESULTS

One hundred and twelve eyes have an average unaided visual acuity of 6/12; 103 eyes have an average visual acuity of 6/9 or better with their present up-to-date refraction, and these eyes also have a best recorded visual acuity of 6/9 from hospital records; 73% of cases see 6/9 or better with or without spectacle correction.

Refractive state. The average spherical lens requirement taken from the refraction has been ±1·1 dioptres, and of those eyes requiring a cylindrical correction the average astigmatic correction is ±1·75 dioptres. This does not include the most recent cases, where the refractive state is changing. In my experience refraction is moderately stable after cataract surgery for 6 weeks.

It is proposed to consider each case with a visual acuity of 6/18 or less individually.

Case 1. The patient had combined penetrating keratoplasty with insertion of a bipod lens for bullous keratopathy. The corrected vision is 6/24, but there are 8 dioptres of corneal astigmatism (the continuous Perlon stitch is still *in situ*).

Case 2. This patient had been noted to have a prior retinal vascular accident; corrected vision is 6/36 and optic atrophy is present.

Case 3. This patient, with high myopia and myopic fundal changes, has a corrected vision of 6/18.

Case 4. A patient of 82, who has suffered vitrous loss at operation, and has senile macular degeneration with a corrected vision of 6/18.

Case 5. A patient with corrected vision of 6/18; there is no obvious reason for the poor visual acuity in this case.

Case 6. A patient who had bullous keratopathy, secondary cataract, and a soft eye after an Elliott's trephine operation many years ago. Surgery included penetrating keratoplasty, cataract surgery reconstruction of pupil, and insertion of bipod lens. The corrected vision is 6/60 with a clear corneal graft.

Case 7. This patient had a corrected vision of 6/18, but the intraocular lens is probably centred too high.

Discussion

Operative complications have been minimal in this series, the greatest problem being removal of all cortical material, especially with an immature cataract. There seems to be no way to reduce this time-consuming procedure without expensive aspiration/irrigation equipment. Maintenance of corneal clarity by continuous irrigation with balanced salt solution and availability of balanced salt solution incorporating glutathione and adenosine may in future further reduce postoperative striate keratitis.

The operative techniques described, incorporating dislocating the nucleus into the anterior chamber and its removal with a vectis, can be carried out with a small 9-mm incision. The lens can, indeed, be inserted through a smaller incision than this in the case of secondary insertion or if phacoemulsification equipment is available. Strong mydriatics can be used pre- and postoperatively as the iris sphincter is not involved in supporting the intraocular lens and their use also facilitates absorption of any cortical remants. Return of visual function is rapid, and the increased safety of a small corneoscleral incision allows early hospital discharge (normally the day after operation).

Surgical uveitis has been minimal, and the total absence of postoperative hyphaema is probably related to the abandonment of peripheral iridectomies. The lens design with the 4-mm optic seems to reduce the likelihood of pupil-block glaucoma, there being no such problem in this series, the thin lenticulus allowing adequate drainage between the pupil sphincter margin and the anterior surface of the prosthesis. Increasing the optic size may increase the possibility of pupil-block glaucoma as well as increasing the weight of the lens.

The series has been free of retinal detachment, but there have been two cases with corneal changes, probably due to surgical trauma. The one case of clinical cystoid macular oedema occurred where vitreous loss with rupture of the posterior capsule was a surgical problem. In my own series of 360 eyes with pupillary lenses cystoid macular oedema occurred in 7 eyes (1·9%). Binkhorst *et al.* (1976) maintain that posterior capsulotomy seems to compromise the protection provided by the capsule to the macula.

Cystoid macular oedema would seem now to be the most feared common complaint of implant surgery. Meredith *et al.* (1976), considering a series of classical intraocular cataract extractions, found cystoid macular oedema occurring in 10% of eyes. These eyes had a visual acuity of less than 20/40.

Dallas (1976) found that in 260 eyes having had plain cataract extraction cystoid macular oedema occurred in 5 (1·8%). Of 200 eyes with iris clip lenses 12 (6%) suffered macular disturbance. Marmion (1976) emphasised the important prognostic implication of the Irvine-Gass type of cystoid macular oedema occurring as a transient episode in about 40% of cataract extractions, and having a relatively good prognosis. He reviewed 750 cases of classical cataract extraction, of which 2·1% exhibited this syndrome. In pseudophakia, however, there is a greater preponderance of Jaffe's syndrome, in which there are definite cystoid changes without oedema and with a less favourable prognosis. Both Dallas (1976) and Binkhorst *et al.* (1976) consider that extracapsular techniques confer some protection to the macular region.

The initial results of this series compare favourably with those of other methods of cataract surgery with or without implantation. Dallas (1976) found that 67% of eyes after plain cataract extraction saw 6/12 or better. In my review (Pearce, 1975) of Choyce's cases of Mark VIII implants 73% saw 6/9 or better, and similarly in reviewing Binkhorst's cases of 4-loop pupillary lenses with intracapsular extraction (Pearce, 1972) 67% of eyes had visual acuity of 6/9 or better.

It is important not to give a prescription for glasses until 6 weeks after surgery. Singh *et al.* (1976) in their series of plain cataract surgery showed that 3 sutures gave the least astigmatism and that refraction was not stablised for 6 weeks after surgery. The average cyclinder on retinoscopy was 1·77 dioptres. They also found that keratometry bore little relation to the refraction result in their cases. On reviewing my series of 360 eyes with pupillary lenses I found that the spherical correction was ±1 dioptre, the cylindrical correction being 1·0 dioptre. It will be interesting in the future to evaluate whether reduction of incision size to 9 mm with 3 preplaced corneoscleral sutures reduces the astigmatic error after surgery.

Various configurations of lens design are now available (Fig. 1*a*, *b*, *c*) and provided there is an adequate inferior capsular bag the 4·7-mm radial tripod lens can be used without an iris suture fixation. Nevertheless, iris fixation gives some stability to the lens and may indeed 'polish the posterior capsule' during normal pupillary function.

Patient satisfaction with the operation has been good, and pupillary function is normal, without complaints of photophobia. (These were especially noted when patients have had a posterior chamber lens with a normally acting pupil in one eye and in the other eye an iris clip lens.) The eye itself looks normal (Fig. 2), and the pupil can be fully dilated for examination of the periphery of the fundus (Fig. 3). It would also seem that there is less tendency for pigment deposit on the anterior surface of the prosthesis than with pupillary lenses, and, of course, there is no danger of erosion of the iris sphincter by

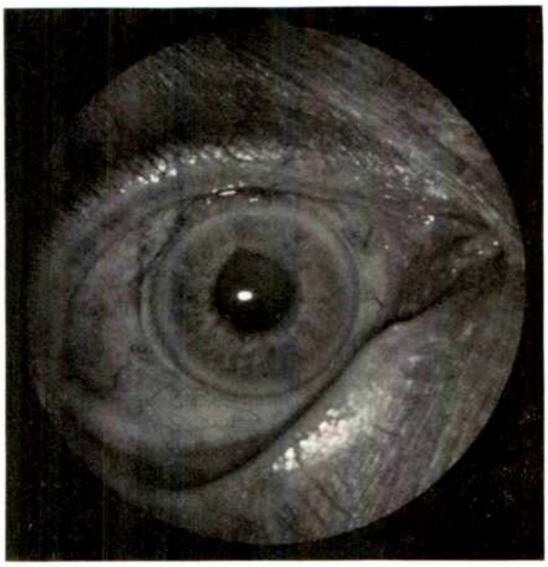

Fig. 2

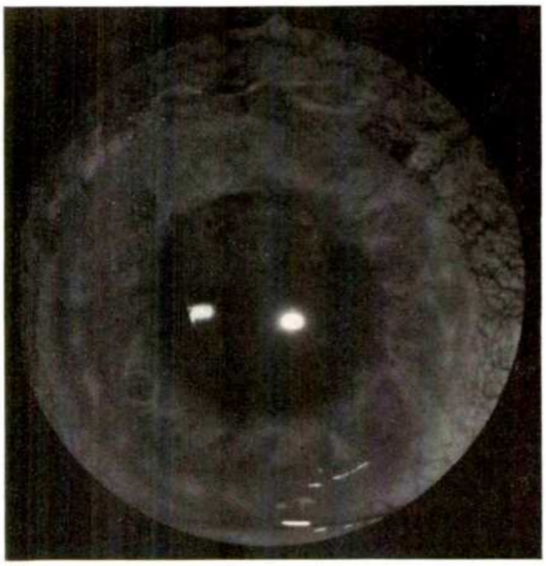

Fig. 3

the posterior loops of an iris clip or iridocapsular lens.

Secondary insertion through a very small incision of about 5 mm can be easily performed when there is an intact posterior capsule or adequate posterior capsule for prosthesis fixation. In these cases, especially with the younger patient, it is politic to select the bipod lens, which is also the lens of choice for combined keratoplasty. It is wise to have available lenses with varying lengths of inferior feet, so that if the pupil is small after extracapsular extraction a lens with 4 mm radial inferior limbs can be used. This allows minimal manipulation within the anterior chamber. Conversely, if the pupil remains large, then a longer length of inferior feet is chosen. The pupil should be round at the end of the operation; if it is still widely dilated acetylcholine drops should be instilled before the eye pad is placed. Dilatation of the pupil can then be begun at the first dressing.

Complications of Ridley's original posterior chamber lens, which weighed 106 mg in air and was 8·35 mm in diameter (approximately 1 mm smaller than the normal crystalline lens), have been summarised by Ridley (1953, 1954, 1958, 1960) as: iritis; occlusion of the pupil by dense inflammatory membrane; late thickening of the posterior capsule, especially in young patients; anterior chamber loss for unknown reasons; secondary glaucoma due to shallow anterior chamber; iris atrophy; and posterior dislocation of the prosthesis. These complications were not evident in the present series of posterior chamber lenses, so it would seem fair to conclude that the use of a lightweight posterior chamber lens with extracapsular cataract extraction is a relatively safe procedure.

I thank Mr E. Ford, Raynor & Keeler Ltd, for his continuing help in the development of lenses and for his line drawings, and Miss J. Walden for her secretarial help.

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Technique of implantation of extrapupillary iris lens: 8 years of clinical experience

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SUMMARY A new type of intraocular lens has been devised. The lens is iris-supported but, in contrast to conventional iris-clip lenses, is fixed at the iris periphery, leaving the pupillary region free. The lens may be implanted either anterior or posterior to the iris plane. Implantation into the posterior chamber is particularly beneficial when combined with an extracapsular extraction. Eight years' experience (189 operations) underlines a number of important advantages of the extrapupillary iris lens. The pupil is not distorted, so that its form and function remain normal; the danger of dislocation is avoided; and the lens may be employed in the presence of an iris coloboma. The supporting prongs of the lens are made of gold and platinum alloys, which add considerably to its tissue tolerance. So far no complication has arisen necessitating removal of such a lens. This new type of intraocular lens offers a combination of efficacy, safety, and technical simplicity.

The 'extrapupillary iris lens' was first mooted in 1968. Although it is an iris-supported lens, the points of attachment are placed at the periphery of the iris away from the pupillary region. As compared to the conventional iris-clip lenses this attachment has major advantages (US Patent No. 3922728) (Krasnov, 1975). The main advantages of the extrapupillary iris lens over the conventional iris-clip lenses are as follows:

(1) The form and function of the pupil remain normal. (2) Dislocation of the extrapupillary lens is rare. The incidence of dislocation of the iris clip lens is 5 to 10% (Fyodorov and Feldman, 1973; Zakharova and Fyodorov, 1973; Nordlohne, 1975). (3) The vitreous face is not damaged by the extrapupillary iris lens because no large supporting loop is introduced behind the iris, so that the chance of vitreous loss is minimised. (4) Mydriatics may be used postoperatively to suppress inflammation, whereas mydriatics may lead to complications with iris-clip lenses (Fyodorov, 1973). (5) The extrapupillary iris lens may be employed in the presence of an iris coloboma (6) Absence of contact of the extrapupillary iris lens with the anterior chamber angle avoids structural and functional damage to this area. (7) The lens design is simple and made of biologically inert materials (highly purified methyl methacrylate with platinum or gold alloys). (8) The surgical procedure is technically uncomplicated. All manipulations are limited to the confines of the anterior chamber.

The general trend of development in the field of intraocular lenses is towards extrapupillary fixation, as is exemplified in the suturing of iris-clip lenses (Worst, 1971) to the periphery of the iris. Ten years ago clinical trials of several types of extrapupillary iris lenses were instituted. The original model had three supporting prongs inserted into punctures at the iris periphery. Two fixation points, however, were found to be ample. A whole family of extrapupillary lenses was tested clinically (Fig. 1), and eventually two were found to be the most practical (Fig. 2).

The first (Fig. 2*A*) has two bayonet-type fixation prongs. The prongs (made of platinum or gold alloys) have pointed ends introduced into corresponding holes in the iris periphery. The correct placing of these holes constitutes a delicate step in surgical technique. If the holes are placed too far apart the fixation of the lens may not be firm enough, especially in mydriasis. If they are placed too close together the pupil may become elongated (which is not dangerous, but cosmetically unsatisfactory). In the second type (Fig. 2*B*) one of the supporting prongs is made in the form of a loop to be sutured to the iris (usually above near the incision); the opposite (distal) prong is the same as in type *A*, and is introduced into a dehiscence in the iris. One of the prongs is thus rigidly attached; the other is

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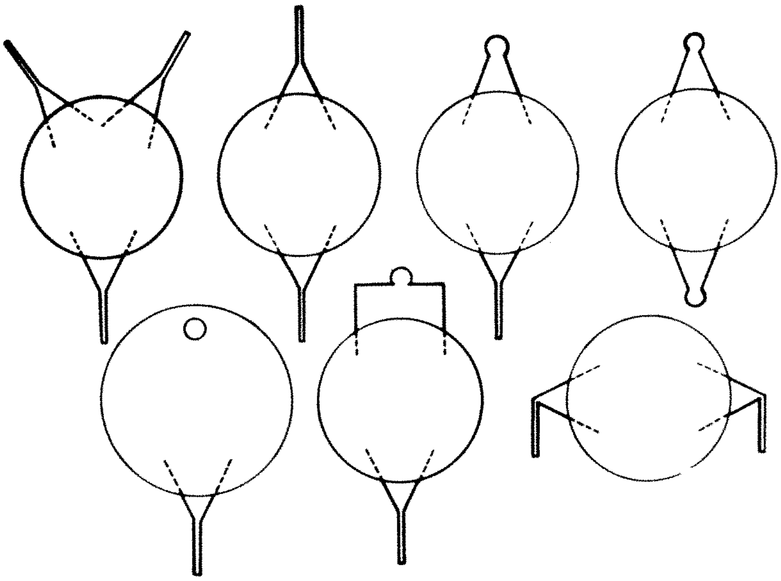

Fig. 1 *A family of extrapupillary iris lenses with different types of supporting prongs*

referred to as the 'sliding' prong. The technique of implantation of the *B* type extrapupillary lens requires more time because of the iris suture, but on the whole the procedure is quite safe in routine practice. The *B* type lens lessens the risk of dislocation. An iris suture, of course, may be inserted through holes in the body of the lens itself as in the Worst 'Medallion' lens. Movement of the iris musculature influences the lens less if the attachment to the iris is well away from the pupil border. In order to make the fixation point as peripheral as possible it is preferable to pass a suture through an 'intermediate' loop-like prong which extends to the iris root. If such a suture to the iris periphery has an attachment to the body of the lens, then the optical portion is of necessity unduly large and heavy.

A small iridotomy is usually done at the site of suturing to sever the iris muscles from the fixation point. The type *B* is especially advantageous in cases with an iris coloboma or traumatic mydriasis and in situations wherein special safety requirements are necessary, for instance, for sportsmen, drivers, or pilots. It is possible to suture the loop-like supporting prongs to the iris, but the complexities of this technique do not seem to justify its routine use. As we pointed out elsewhere (Krasnov and Orlova, 1969) an extrapupillary iris lens may also be placed in the posterior chamber.

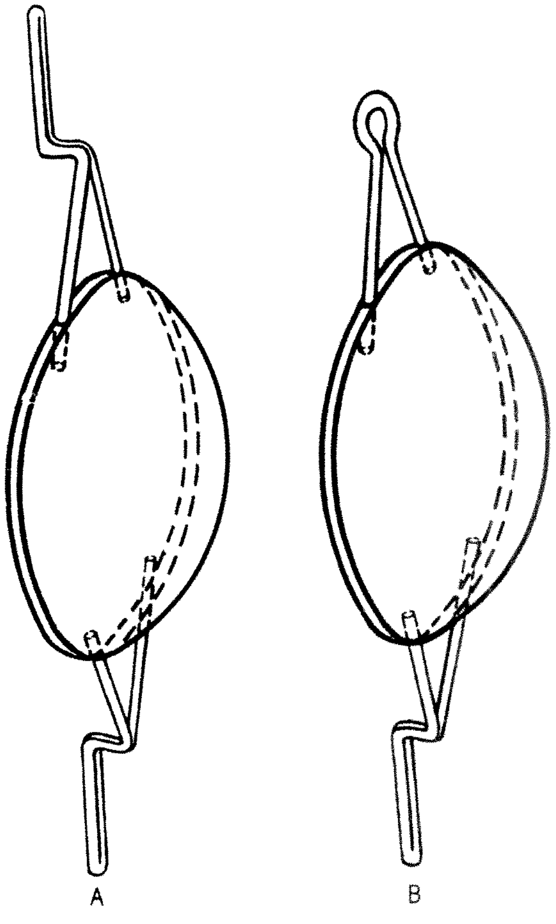

Fig. 2 *Bayonet-type of extrapupillary iris lens* (A) *and lens with a loop-like prong for an iris suture* (B)

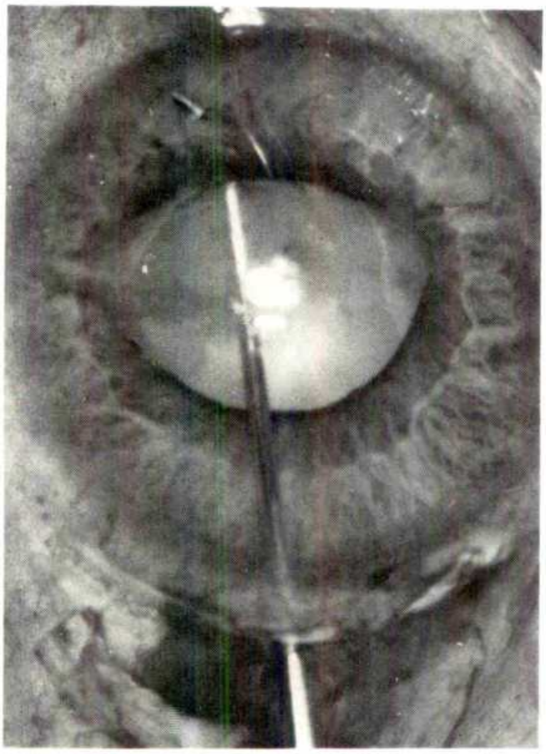

Fig. 3 *Making of distal iridopuncture by a Sato knife*

A total of 189 extrapupillary iris lens implantations have been inserted and followed up during the last 8 years. In no case has a lens had to be removed because of complications. There were no cases of bullous keratopathy. During the first years of experience in 9 cases the upper supporting prong was displaced soon after insertion owing to poor surgical technique in placing the iridopunctures. As soon as the cause was recognised, this surgical error was avoided.

The primary aim of this paper is to describe the essential elements of the surgical technique for the implantation of an extrapupillary iris lens. Standard surgical techniques such as adequate hypotony of the eye before operation, proper anaesthesia, and perfect suturing of the incision are taken for granted, and only specific points are described. All types of extrapupillary lenses can be implanted simultaneously with cataract extraction or as a separate procedure later.

Operative technique

Iridopunctures. A pinpoint hole should be made at the periphery of the iris before the anterior chamber is emptied. The anterior chamber is entered by a Sato-knife (or a similar type of needle/knife), usually at the upper limbus. The instrument then is slowly carried across the anterior chamber to the pupil, and from here on it passes under the iris to the point of planned iridopuncture (Fig. 3). At this point the shaft is rotated through 90° and the blade of the instrument cuts through the iris from behind (towards the cornea). The position of the iridopuncture must be approximately half-way between the pupillary margin and the limbus of the same meridian. It is important to enlarge the opening (sometimes by a blunt spatula) to make it wide enough to accept the supporting prong of the lens without unnecessary trauma to the iris. If the anterior chamber is accidentally emptied during the manoeuvre it is more difficult to perform an iridopuncture. The anterior chamber should then be refilled to its full depth (if necessary, some temporary sutures can be inserted to prevent the escape of fluid) and the procedure repeated in exactly the same way. A good iridopuncture may be produced by laser (Krasnov, 1973) preoperatively.

If the *A* type of extrapupillary iris lens is used (bayonet type of fixation of both supporting prongs), then a second iridopuncture is carried out after the incision into the anterior chamber has been completed. A second (proximal) iridopuncture is easy to perform because it is situated quite close to the incision.

The iris is grasped by fine forceps, lifted up slightly, and punctured either by a Sato-knife or pinched by Vannas scissors. If the *B* type is used, an iris suture is placed at the same point to secure the proximal supporting prong of the lens later (see below).

A Supramid or nylon thread can readily be used, but sutures of 20 to 25 μm wire (gold and platinum alloys especially) are superior in our hands. A basal iridectomy or an iridotomy is often performed at this meridian, and then the suture is conveniently passed through the distal (central) edge of the iris coloboma.

As already indicated, when a cataract extraction is completed and the pupil made miotic, all the manipulations with an extrapupillary iris lens are confined to the anterior chamber entirely. This is a factor of great safety, as no supporting loops are pushed behind the iris into the vitreous chamber as is the case with the iris-clip lenses.

Manoeuvring of the lens into the anterior chamber. Originally, the lens was slid into the anterior chamber with its 'bayonet' prong pointing to the site of the iridopuncture (the pupil being avoided so as not to injure the vitreous face). The main technical inconvenience of this approach was the tendency of the pointed end of the prong to become entangled in the iris tissue. It proved both easier and safer to introduce the lens with the supporting prongs in the plane of the corneoscleral incision and pointing to 3 and 9 o'clock. The lens is then rotated in the anterior chamber, so that the bayonet prong approaches the iridopuncture laterally. In this way the tendency for the prong to be entangled by iris folds is lessened.

Manipulations with the lens inside the anterior chamber. 'Hydraulic separation' of the structures of the anterior segment of the eye. When an intraocular lens has been manoeuvred into the anterior chamber damage to the cornea, the iris, and the vitreous body must be avoided. If the eye is hypotonic the lens slides in easily, and the supporting prongs go into the preplaced holes without difficulty. If the iris is forward towards the cornea, there is a tendency for iris tissue to obstruct the ends of the supporting prongs. Occasionally difficulties are met with in placing a bayonet prong if the accepting iridopuncture is too small. The Binkhorst forceps then prove helpful.

The best method of coping with such problems is to restore the normal depth of the anterior chamber with reposition of all its structures. It is possible, for instance, to put a lens into the anterior chamber, seal the wound, fill the anterior chamber with saline, and then proceed with the positioning of the lens using thin spatulae. Alternatively, 'hydraulic restoration of the anterior chamber' is most efficient. The incision is not sutured, but adequate separation of the iris and cornea is achieved by a constant inflow of fluid. The assistant fills the anterior chamber while the surgeon concentrates his attention on manipulating the probe (Fig. 4). After the bayonet prong is secured in the iris hole, the lens must be properly centred in the anterior chamber.

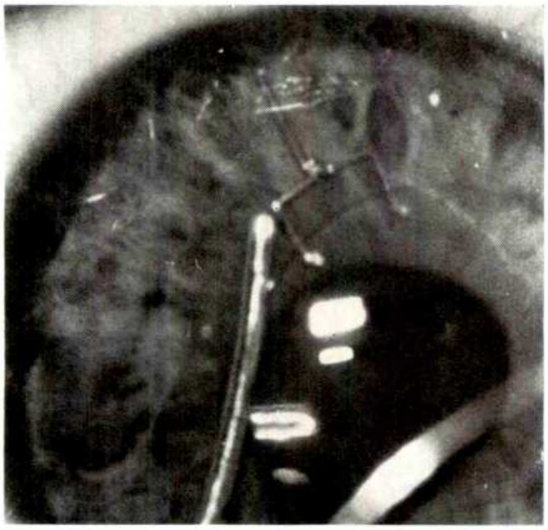

Fig. 4 *Hydraulic separation of the cornea and iris as distal supporting prong is being manoeuvred into the iris puncture*

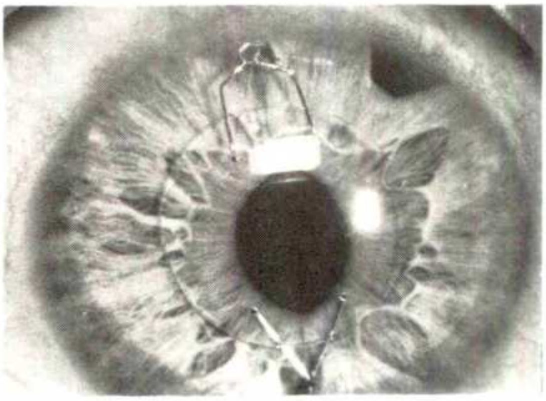

Fig. 5 *End result of implantation of extrapupillary iris lens* (B) *with sutured upper supporting prong*

Fixation of the proximal supporting prong (versions A *and* B*). Version* A *(two bayonet prongs).* When the distal prong is secured, the upper part of the iris is pulled out of the wound slightly by iris forceps. The proximal iridopuncture can thus be moved to the end of the proximal prong, which finally slides into it. After that the iris is gently reposited.

Version B *(one bayonet prong, one loop for suturing).* The iris suture is placed before the intraocular lens is positioned in the anterior chamber. The end of this suture is passed through the loop (but left untied) prior to the manipulations described above. After the distal prong of the lens is secured and the lens itself centred the only step left is to tie the knot. If sutures of gold or platinum alloys are used 1 knot is sufficient. Nylon or Supramid sutures are tied with 2 or even 3 knots. The end of the cut suture must not touch the cornea or the structures of the anterior chamber angle. Suturing of the lens gives an additional element of safety; no dislocation was encountered with this type of fixation (Fig. 5).

Technique of extrapupillary lens implantation into the posterior chamber. The *B* type of extrapupillary iris lens (one bayonet prong, one loop for suturing) is fairly well suited for implantation into the posterior chamber. As is known, this is especially advantageous with an extracapsular lens extraction. In this particular situation there is no need for iridopunctures.

The lens is gently pushed in through the incision and then through the pupil (with the bayonet prong directed forward into the posterior chamber). A suture should then be passed through the loop-like prong to control the lens position. When the lens is completely covered by the iris the bayonet prong perforates the lens capsule at its equator. After the lens is properly centred its proximal (usually, upper) loop-like prong is sutured to the edge of the iris coloboma.

It is commonly considered that the position of the lens in its natural place, especially in combination with an extracapsular extraction of cataract, has the advantages of lesser degrees of aniseikonia and less risk of retinal and vitreous complications.

Final stages of the operation. A watertight closure of the wound is imperative. Special attention should be given to evacuation of all traces of blood from the anterior chamber. Filling the anterior chamber with air may be risky. Pupillary blockage is particularly undesirable in the presence of an intraocular lens (and may among other things predispose to lens dislocation). Air injection should be recommended. After the toilet of the incision and the anterior chamber is completed, the air is replaced by saline or (preferably) by a balanced salt solution. Implantation of the extrapupillary iris lens into both the anterior and posterior chamber of the eye can readily be combined with phakoemulsification (Krasnov *et al.*, 1975).

In conclusion it may be stated that the extrapupillary iris lens is one of the most practical and safest solutions to the problem of intraocular lens implantation.

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British Journal of Ophthalmology, 1977, **61**, 321-326

Aphakic macular oedema following prosthetic lens implantation*

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From the Bristol Eye Hospital, Lower Maudlin Street, Bristol

SUMMARY Fluorescein angiography of the iris was performed on patients with plastic lens implants with cystoid oedema of the macula, and the nature of the vascular changes was compared with controls provided by patients who did not have macular disease. Densitometry was used to quantitate leakage of fluorescein dye into the anterior chamber in residual angiograms 5 minutes after injection. Cystoid oedema was associated with marked increase in vascular permeability of the iris in the patients with implants, and in aphakics without implants, but to a lesser degree. Although it cannot be concluded that implants themselves cause either the increase in permeability or the onset of macular oedema, the presence of such implants must be considered an additional hazard in an eye which is already at risk. Iris angiography can be used as a diagnostic aid in patients in whom macular oedema is suspected. A persistent increase in permeability associated with a reduction in visual acuity should act as a warning of further visual loss and of eventual cystoid macular degeneration.

With the increasing use of prosthetic lens implantation following cataract extraction, the nature and incidence of operative and postoperative complications are being investigated in more depth. Postoperative anterior uveitis, retinal detachment, acrylic lens dislocation, glaucoma, bullous keratopathy, and cystoid macular oedema have all been reported, but it is the macular disease which is particularly a cause for disappointment to the patient and concern for the ophthalmic surgeon.

Macular oedema and visual loss following cataract extraction were originally described by Irvine (1953) as being associated with irritability of the eye and also rupture of the anterior hyaloid membrane leading to vitreous strands adhering to the section. Gass and Norton (1969) stated that adherence and traction were not a necessity for the development of macular oedema but when present tended to worsen the condition. In a study of macular disturbance 6 weeks after cataract extraction (Hitchings *et al.*, 1975) transient oedema occurred in 50% of patients examined. No such changes developed in a group of controls who had glaucoma surgery. The authors considered the major differences between the two groups were the actual cataract extraction and the presence of postoperative vitreous inflammation. Assessment 6 months after cataract extraction showed that 10% had a corrected visual acuity of 6/12 or 6/18, while in the remainder the acuity was 6/9 or better. Cataract extraction may frequently induce macular oedema, which generally resolves but in a small proportion of cases leads to a varying degree of visual loss.

The incidence of cystoid oedema of the macula in pseudophakia has been variously stated to be 5% (Pearce, 1972), 12% (Binkhorst and Leonard, 1967), 19% (Jardine and Sandford-Smith, 1974), and 7% (Dallas, 1976), which are all greater than the 2% incidence following plain intracapsular cataract extraction in a series of 200 patients. Since the frequency and severity of cystoid macular oedema are known to be greater in patients with implants than in aphakic patients without implants, the question arises whether the implant is responsible.

Iris angiography has frequently been used to assess the state of the iris vasculature in a number of diseases (Mitsui *et al.*, 1969; Bron and Easty, 1970; Vannas, 1969; Cobb *et al.*, 1970; Easty and Chignell, 1973). In a group of 9 patients with cystoid macular oedema after intracapsular cataract extraction moderate to massive leakage of fluorescein dye

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was noted on iris angiography (Kottow and Hendrickson, 1975). In order to determine how the iris vasculature is affected by acrylic lens implants, and its possible relation to cystoid macular oedema, iris fluorescein angiography was performed on groups of patients with and without macular oedema.

Prostaglandins are known to act as one of the mediators for the responses of the eye to trauma (Ambache *et al.*, 1965; Cole and Ungar, 1973). Iris-suspended lenses are not perfectly stable. Because of this they may cause mechanical stimulation, which could produce detectable increases in pharmacological mediators in the intraocular fluids, which in turn may play a role in the production of macular disease. As a supplementary study, therefore, prostaglandin-like activity was sought in aqueous humour taken from patients with cystoid macular oedema who were undergoing further operative procedures. Experimental studies were also performed on aqueous humour taken from rabbits from which the crystalline lenses had been removed and replaced with acrylic implants.

Materials and methods

Iris fluorescein angiography studies were performed on 40 patients after cataract extraction at least 6 months previously, with and without signs of cystic macular oedema and with or without acrylic implants (Table 1). Acrylic lens implantation was performed by one of us (N.L.D.) using Binkhorst (8 eyes) or Federov iris-clip lens (21 eyes) or the Ridley anterior chamber implant (12 eyes, also referred by Mr C. A. Brown). A full ocular examination was carried out on all patients prior to the study. The intraocular pressures were measured and the state of the iris and the anterior chamber was examined. The retina and vitreous were examined in detail with the slit-lamp microscope. It was not possible to use retinal fluorescein angiographic photography to determine whether the signs were typical of cystoid macular degeneration, because pupils could not be safely dilated with mydriatics; however, confirmatory evidence was obtained with indirect ophthalmoscopy fitted with appropriate filters after the intravenous injection of fluorescein dye. In all affected patients there had been good postoperative visual recovery, though this was followed by visual deterioration some months later. No cause other than macular oedema was found to explain the loss of vision.

Iris angiography was performed by a standard technique (Easty and Bron, 1971) in patients not less than 6 months after operation. Photographs were taken at 2-second intervals for periods of 30 to 60 seconds, and residual photographs were taken after an interval of 5 minutes. Ilford FP4 film was processed according to a standard method using developer (Qualitol, May & Baker) for 10 minutes at a dilution of 1 in 20 at 68°F (20°C). Contact sheets were routinely printed (Ilford PQ Universal Developer for 2 minutes at 1 in 9 dilution at 68°F (20°C)). The iris angiograms were examined for signs of vascular abnormality and particularly for leakage of fluorescein into the iris stroma or anterior chamber. The magnitude of the fluorescence that occurred was measured directly from the angiogram with the aid of a standard densitometer.

Table 1 *Case selection for iris fluorescein angiography*

		Number of eyes
Controls		
Phakic		29
Aphakic:	without macular oedema	7
	with macular oedema	4
Aphakics with implants		
Iris clip without macular oedema		14
Iris clip with macular oedema		15
Ridley implant without macular oedema		8
Ridley implant with macular oedema		4

Prostaglandin assays were performed on aqueous humour taken from 4 patients all of whom had plastic implants and 3 of whom had cystoid macular oedema. Serial measurements were also performed on fluid taken from the anterior chambers of 4 rabbits, 2 having had plastic implants following lens removal, and 2 having had simple removal of the lens. Samples were extracted for prostaglandins with ethanol acidified with formic acid followed by chloroform. They were then assayed against PGE 2 for prostaglandin-like activity on rat stomach strips (Vane, 1957) suspended in Krebs' solution at 37°C.

Results

IRIS ANGIOGRAPHY IN THE IMMEDIATE POSTOPERATIVE PERIOD

Postoperative angiographic studies showed that patchy leakage of fluorescein occurred into the iris stroma from dilated radial vessels in all patients investigated, and this was then followed by diffusion of dye into the aqueous humour. The changes occurred both in the presence and in the absence of an implant. The leakage persisted for between 6 weeks and 3 months and then was followed by a return to a normal angiographic appearance.

ANGIOGRAPHY FOLLOWING INTRACAMERAL IMPLANTS WITHOUT MACULAR OEDEMA

In the absence of macular oedema patients with intracameral implants showed no evidence of a disturbance in the vascular physiology of the iris when examined by fluorescein angiography.

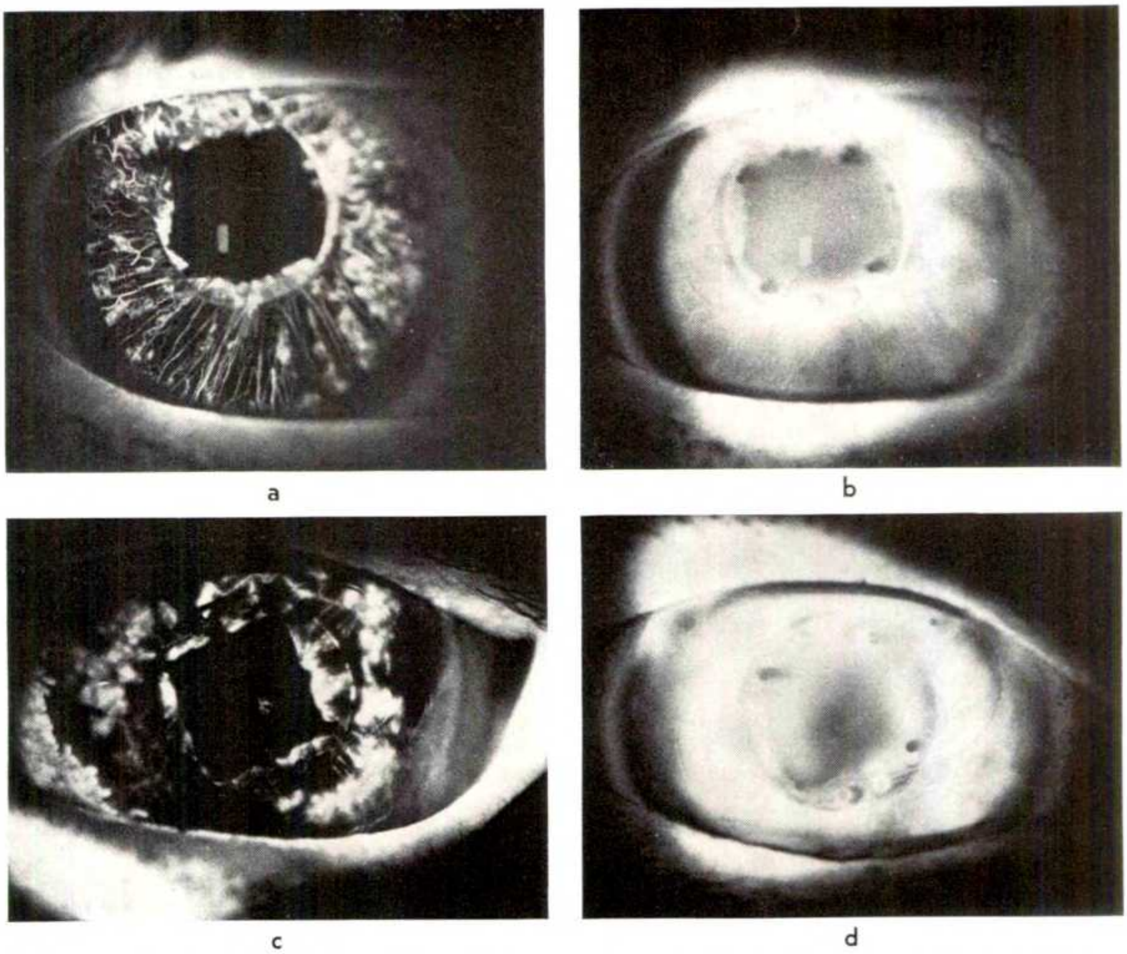

Fig. 1 (a *and* c) *Iris angiograms 20 seconds after injection demonstrating vascular dilatation and early leakage in 2 patients with iris-clip implants and cystoid macular oedema;* (b *and* d) *Residual angiograms in the same patients 5 minutes after injection, showing pronounced leakage into the anterior chambers*

ANGIOGRAPHY FOLLOWING INTRACAMERAL IMPLANTS WITH CYSTOID MACULAR OEDEMA

Nineteen patients had clinical evidence of cystoid macular disease; of these 14 had massive leakage of fluorescein from the iris vessels, 4 had marked leakage, and 1 had only moderate leakage. Fig. 1 shows the appearance that was found in 2 patients who had developed cystoid macular oedema, in both of whom the postoperative visual acuity had been good though it was subsequently followed by visual deterioration. During the early transit of the dye iris vessels are notably dilated, and there is leakage into the iris stroma. Residual angiograms show that there is also diffusion into the anterior chamber, which masks the fluorescing vessels of the iris.

CYSTOID MACULAR OEDEMA IN APHAKICS WITHOUT LENS IMPLANTS

Though in 4 patients in whom macular oedema had been confirmed by retinal angiography there was a moderate leakage into the iris stroma and anterior chamber, it was not so severe as when macular disease was accompanied by lens implantation.

DENSITOMETRY

Densitometric measurement of the residual fluorograms 5 minutes after injection showed that patients with cystoid macular degeneration had marked fluorescence in their anterior chambers, whereas the iris vasculature in patients without macular disease showed no difference from the vasculature in the normal or aphakic eye (Fig. 2). Iris colour did not

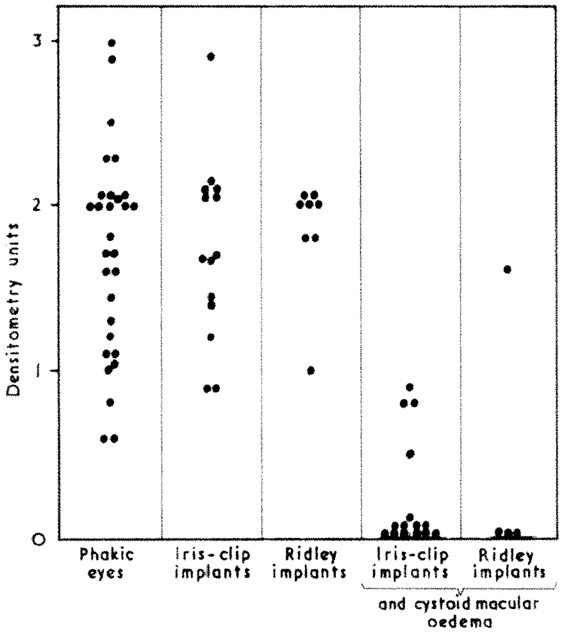

Fig. 2 *Densitometry measurements of the residual iris angiograms in patients with cystoid macular oedema, compared with controls*

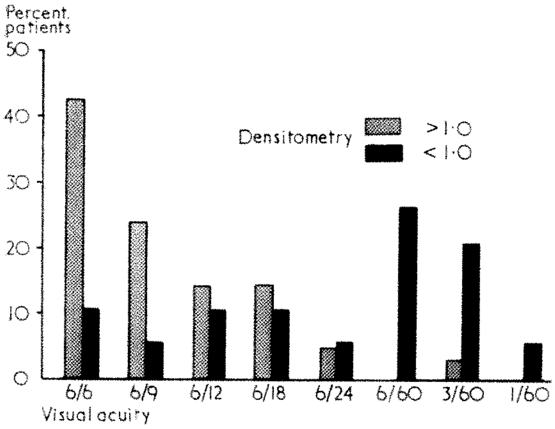

Fig. 3 *Comparison of percentage distributions of visual acuity in 2 groups of patients; those with densitometry > 1·0, and those with measurements < 1·00*

show correlation with the degree of fluorescein leakage in any of this group.

Fig. 3 demonstrates the distribution of visual acuity in two groups of patients—those with readings greater than unity (who had mild to moderate leakage) and those with readings less than unity (where the amount of leakage of dye was marked). Twenty (95%) of 21 patients with mild to moderate leakage had a visual acuity equal to or better than 6/24, while in 20 patients with severe leakage 58% had visual acuities equal to or less than 6/60 ($P<0{\cdot}01$, Fisher's exact probability test).

PROSTAGLANDIN ASSAYS

Assays for prostaglandin E1 and E2 in aqueous humour taken from 3 patients with macular oedema before operations on the same eye did not show raised levels. Similarly, assays performed on aqueous humour taken from two Dutch white rabbits with Federov implants showed no elevation when compared with levels in two controls in which only the crystalline lenses had been removed. The measurements were made 6 weeks after the operations.

Discussion

The results of the survey suggest that cystoid macular oedema in patients with a prosthetic lens implant is associated with persistent dilatation and increased permeability of the iris vessels. Cystoid macular disease is both more severe and more prevalent in these patients, and it seems possible that it could be the apposition of the implant to the iris vessels that may be indirectly responsible.

Many factors have been implicated in the causation of persistent aphakic macular oedema (Table 2). Vitreous complications during surgery are a known precipitating factor, as are the lens removal itself, postoperative vitritis, and systemic vascular disease (Hitchings *et al.*, 1975).

Table 2 *Possible influences in the pathogenesis of cystoid macular oedema*

In aphakia	
Host factors:	age, sex, occupation, systemic disease (diabetes mellitus)
Ocular factors:	aetiology of cataract, associated disease (retinal vein occlusion, uveitis), previous surgery, innate predisposition
Surgical factors:	type of operation (intra- or extra-capsular), technique, complications (e.g., vitreous loss or inclusion in section, etc.)
Postoperative factors:	uveitis, vitritis, vitreous traction, iris prolapse, etc.
Therapeutic:	topical adrenaline drops
In aphakia following plastic lens implant	
Surgical factors:	increased intraocular manipulation
Postoperative factors:	dislocation, uveitis, further surgery
Factors related to the implant:	method of sterilisation iris-clip movement toxicity of plastic antigenicity of plastic

Plastic implants could provide a superadded factor which might affect the macula in a number of ways. Among these should be considered the influence of recurrent episodes of minor trauma, particularly in iris-supported lenses, the toxicity of the component parts, and the antigenicity of these parts.

In the patients with cystoid macular oedema operative and immediate postoperative complications were not a factor. It is conceivable that the continuing wobble in iris-supported lenses may stimulate neurogenic reflexes which would result in vasodilatation of the iris vessels, with a similar response in the ciliary body and elsewhere. At the same time such minor trauma could result in the production of pharmacologically active amines—for example, histamine, 5-hydroxytryptamine, bradykinin, and prostaglandin—which would also act to maintain the vessels in a state of increased permeability and might in themselves be significant in the production of macular oedema. However, bioassay of one of these substances (prostaglandin) in anterior chamber fluid taken from patients with cystoid oedema undergoing further operative procedures following lens implantation did not show a rise in level.

Implants are composed of polymethylmethacrylate, which does not undergo depolymerisation, in contrast to some other plastics, monomer breakdown products of which produce toxic sequelae in eyes. The lack of toxicity is supported by studies carried out by Galin *et al.* (1975), in which cell cultures were not affected by the presence of the plastic, in contrast to which cells failed to grow or showed cytopathic effects in the presence of the polyamide loops.

One way in which plastic implants may create inflammation is by an immunological route, for with the breakdown of the blood-aqueous barrier in the vessels of the iris the anterior chamber is no longer a privileged site. Acrylic materials are known to be good skin sensitisers, and it is possible that both cell-mediated and humoral immunity may be involved in the reaction. It is the humoral response which results in production of such mediators of inflammation as histamine, slow-reacting substance, serotonin, prostaglandins, kinins, lysosomal enzymes, and neurotrophic polypeptides. Certainly an immunological reaction is suggested in the occasional patient when there is a preferential adherence of inflammatory cells to the implant forming precipitates, which are probably lymphocytes or macrophages. It is in these cases that keratic precipitates do not necessarily form. We have noted, however, that in patients showing these reactions there is no evidence of cutaneous hypersensitivity when they are patch-tested to acrylic materials, neither do they demonstrate antigen-stimulated *in vitro* lymphocyte transformation.

The production of cystoid macular oedema in patients with lens implants is therefore multifactorial, but probably the lens itself is a contributing factor. The possible relation of minor trauma to the iris diaphragm is suggested by the fact that preliminary results of iridocapsular implants, where such trauma would be less severe, show a reduction in its incidence. Although the plastic materials used are unlikely to be toxic, because they are known to be antigenic an immunological mechanism remains a possibility.

Florescein angiography of the iris is of value in assessing the response of the ocular tissues to implants and can be of help in the diagnosis of macular disease in its preliminary stages. We are routinely examining postoperative patients by this method, and in cases of persistently increased vascular permeability associated with variable visual acuity early removal of the lens is considered as a preventive measure to reduce the visual loss caused by persistent macular oedema.

We sincerely thank Mr Christopher Dean Hart and Mr Anthony Makepiece for their advice and help, and Mr J. Morgan for photographic assistance. We acknowledge the help of Mr C. A. Brown, who allowed us to examine his patients. We are grateful to Dr Alan Rogers and his staff, who kindly estimated prostaglandin levels in aqueous humour.

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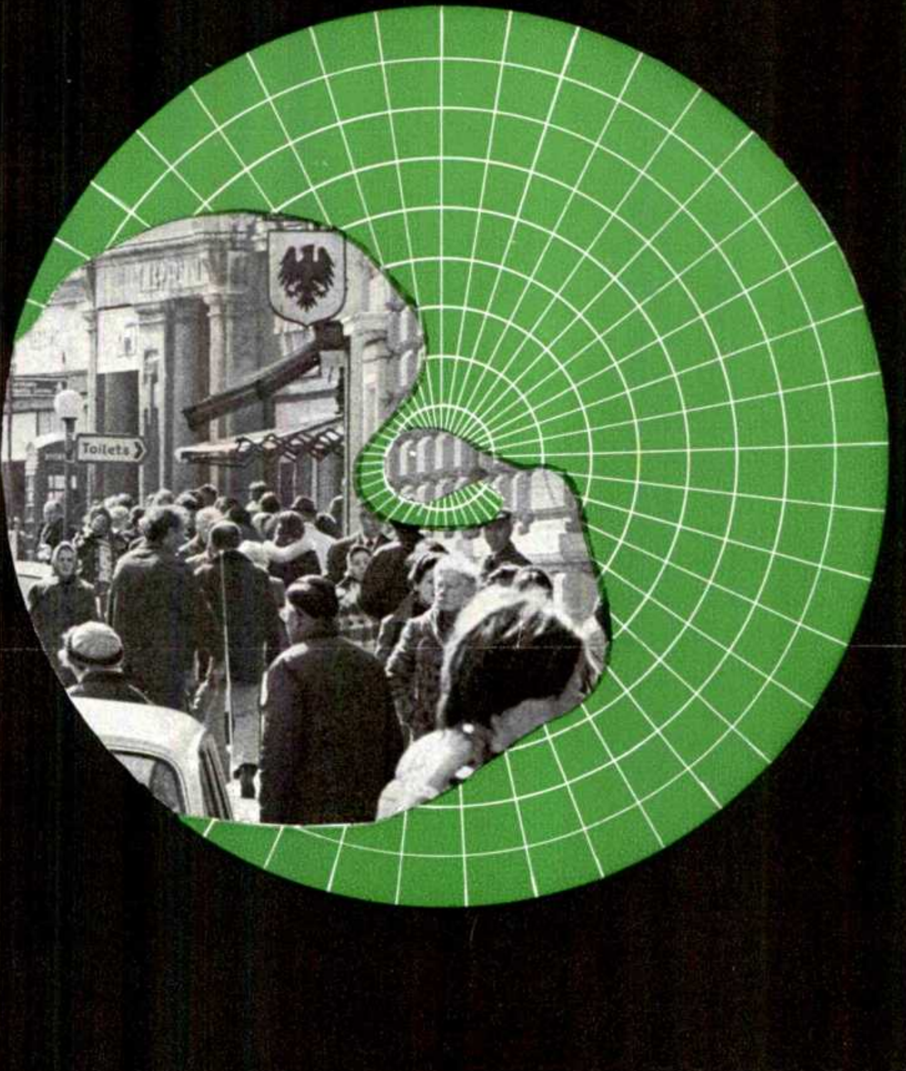

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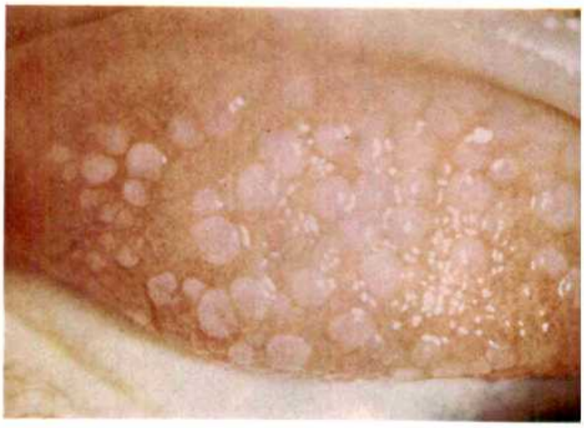
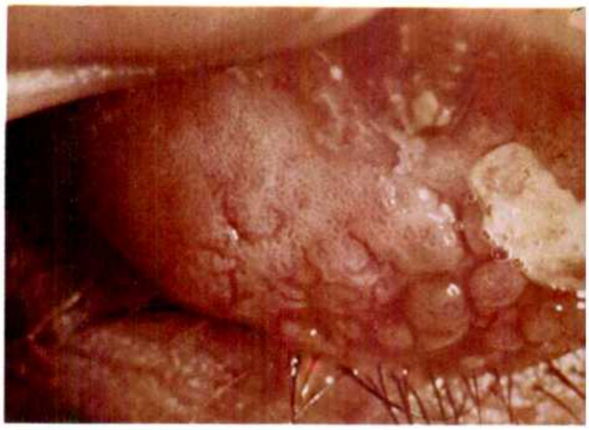
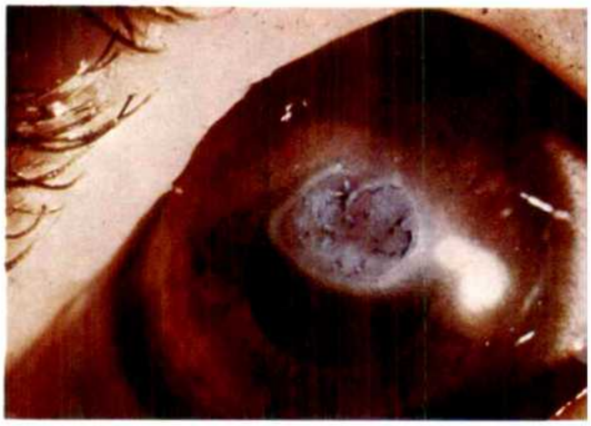


Right upper tarsus of adult patient with vernal kerato-conjunctivitis showing 'cobblestones' due to giant compound papillae.



Upper tarsal plate in active vernal disease. Note fine lace-like scarring and profuse mucopurulent discharge.



Indolent vernal corneal ulcer stained with alcian blue to demonstrate mucous deposition.

Photographs first published in Clinical Allergy (1972) **2** 99-107. Reproduced by kind permission of the publishers.

British Journal of Ophthalmology, 1977, **61**, 327–328

Posterior dislocation of an intraocular lens implant and its removal

A. M. CHOWDHURY AND J. F. BRAS

SUMMARY The cause of dislocation of an intraocular lens is a direct blow or jerk, and dislocation may complicate both iris-supported and capsule-supported lenses. In capsule-supported lenses the implant dislocates towards the anterior chamber but in iris-supported lenses the dislocation is posterior. A technique for removal of a posterity dislocated lens is described.

In 200 cases of successful intraocular implants in the last five years three cases of dislocation of the lens have occurred, an incidence of 1·5%. One was capsule-supported and the other two were iris-supported.

The prime cause of dislocation of these lenses is a direct blow or jerk in association with a lax iris sphincter. In one case a jerk due to physical exercise caused an anterior dislocation of a capsule-supported implant lens. The other two cases involved iris-supported implants, and the lenses dislocated posteriorly towards the vitreous cavity. In one the intact vitreous face held the implant against the iris; in the other the vitreous face was broken and the lens sank to the bottom of the vitreous chamber.

Case report

A male 51 years old developed a right monocular cataract over a two-year period. There was no history of injury or any obvious cause. In September 1975, after intracapsular extraction with peripheral iridectomy, a Binkhorst iris clip type of implant was used. Postoperative progress was satisfactory, and his visual acuity improved to 6/6 in that eye. Unfortunately in March 1976 his hand slipped while pulling and hit his right eye with considerable force. This caused the implanted lens to dislocate posteriorly into the vitreous cavity. The vitreous face was broken and the lens sank into the fluid vitreous. The position of the lens in the vitreous cavity altered with every movement of the head and of the globe and with every change of position of the body in space.

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Removal technique

The pupil was fully dilated, and retrobulbar anaesthesia was induced. Traction sutures were employed on the lids along with a superior rectus bridle suture. The patient was then turned over and made

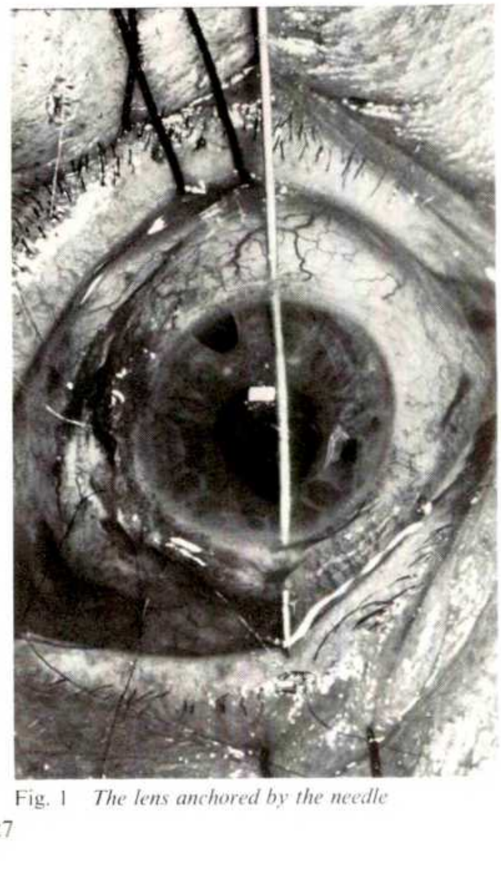

Fig. 1 *The lens anchored by the needle*

to lie flat in the prone position with his head overhanging the top of the table. This procedure brought the dislocated pseudophakia downwards due to gravity, and a set of loops protruded into the anterior chamber through the dilated pupil.

To anchor the lens in that position an approach had to be made from below, and a needle (made from an ordinary retrobulbar needle) was passed through the limbus at the 1 o'clock position into the anterior chamber and through to the limbus at 7 o'clock. This was the most convenient position in this particular case, enabling the needle to pass through the loops of the implant and anchor it firmly (Fig. 1).

After the lens was anchored the patient was turned into the supine position. Sterile drapes were positioned and an ab-externo approach was made at the lateral limbus from 8 o'clock to 12 o'clock under a limbus-based conjunctival flap. A pair of curved, toothed iris forceps was introduced into the anterior chamber and the loops of the implant were grasped. The fixing needle was then withdrawn and the implant extracted slowly.

To close the wound the cornea was sutured with virgin silk and the conjunctiva with fine catgut. Postoperative progress was satisfactory, and the patient was discharged home within a week of the operation. Vision later improved to 6/12 Snellen and N6 with a suitable reading addition. The patient has subsequently been fitted with a contact lens.

British Journal of Ophthalmology, 1977, **61**, 329–333

Pseudophakic pupillary-block glaucoma

DAVID WERNER AND MARTIN KABACK
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SUMMARY Four cases of iris-supported pseudophakic pupillary-block glaucoma were presented. Pupillary-block glaucoma is the first postoperative complication seen following the implantation of an intraocular lens, and in our series occurred at an incidence of 3·8%.

A short review was made of pupillary-block glaucoma with all types of intraocular lenses, with emphasis on the iris-supported lens. The role of inflammation, haemorrhage, and vitreous and lens material in obstructing aqueous flow at the pupil and peripheral iridectomy site was emphasised. Pitfalls in the diagnosis and management of this condition were reviewed. Methods of prevention and treatment were reviewed with emphasis on early mydriasis, along with carbonic anhydrase inhibitors and hyperosmotic agents as a primary medical treatment. Iridectomy, laser iridotomy, or transfixation of the iris was mentioned as a surgical treatment.

Pseudophakic pupillary-block glaucoma was reported by Ridley (1960). Interest at this time centred on posterior chamber lenses. However, Boberg-Ans (1961), Barraquer (1962), and Bresnick (1969) had focused attention on the same complication occurring with anterior chamber lenses. This unique form of glaucoma was briefly described by Nordlohne (1975) in association with iris-fixation lenses and iridocapsular lenses.

A total of 106 iris-supported lenses were inserted as primary procedures at the Jewish General Hospital in Montreal from March 1975 to November 1975. The most frequent and serious complication was pseudophakic pupillary-block glaucoma. It occurred in 4 patients for an incidence of 3·8%.

Although the problem has been identified in the literature, a thorough description of the entity is lacking. It is the purpose of this paper to review pseudophakic pupillary-block glaucoma, to illustrate the pitfalls in the diagnosis and management, and to recommend a simple method of prevention and treatment.

Case reports

CASE 1

A 75-year-old Caucasian female was admitted to the Jewish General Hospital on 14 August 1975 for cataract extraction and lens implantation. Physical examination showed no significant abnormalities, with the exception of the eye findings. The best corrected visual acuity was 20/70 in the right eye and 20/400 in the left eye. Slit-lamp examination revealed anterior cortical opacities as well as nuclear sclerosis in the left lens. Intraocular pressure was 10 mmHg in the right eye and 8 mmHg in the left eye.

On 15 August 1975 the patient had an uncomplicated intracapsular cataract extraction in the left eye. The anterior chamber was entered through a 2-planed incision which was extended until it encompassed 180°. Alpha-chymotrypsin was used. A platinum clip iris-fixation lens was inserted into the anterior chamber and secured through a superior peripheral iridectomy. Acetylcholine chloride was injected into the anterior chamber to position the lens. The section was closed with 8 interrupted 8–0 silk sutures.

On the first postoperative day there was moderate epithelial oedema, a shallow anterior chamber, and an intraocular pressure of 44 mmHg. Therapeutic dosages of oral acetazolamide and intravenous mannitol were started. The intraocular pressure then fell to the mid-30s. By the fifth postoperative day, on the same medical therapy, the clinical situation was unchanged and the surgeon elected to perform a vitreous aspiration. 1·5 ml of fluid vitreous was aspirated through the surgical wound and the anterior chamber deepened. The acetazolamide and mannitol were discontinued. On the sixth postoperative day the intraocular pressure was 20 mmHg.

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Twenty-four hours later, however, the intraocular pressure had risen to 50 mmHg. The anterior chamber had shallowed and there was iridocorneal touch inferiorly. Acetazolamide and mannitol were again given. On the eighth postoperative day, mydriasis with phenylephrine 10% and tropicamide 1% was attempted. A good mydriatic response was achieved, but vitreous presented between the lens margin and the pupil in all areas except the inferior temporal quadrant. The intraocular pressure remained in the high 40s. On gonioscopic examination iris bombé was noted and the angle structures could not be visualised. On the ninth postoperative day the intraocular lens implant was removed. The intraocular pressure, however, remained elevated, and ecothiopate iodide (Phospholine Iodide) 0·06% twice a day was required to bring the intraocular pressure in the range of 20 mmHg. By October 1975 the intraocular pressure had stabilised in the high teens, controlled by 1 drop of 0·125% ecothiopate iodide daily.

Subsequently the intraocular pressure became elevated and was uncontrolled on maximum medical therapy. The patient required a combined trabeculectomy and anterior vitrectomy to lower the pressure. On her most recent examination the best corrected visual acuity was 20/400 and the intraocular pressure was 22 mmHg on pilocarpine 6% every 4 hours and acetazolamide 250 mg q.i.d.

CASE 2

A 68-year-old Caucasian male was admitted to the Jewish General Hospital on 10 April 1975 for cataract extraction. He was a mild diabetic and hypertensive, under good management. Physical examination was normal, with the exception of the ocular findings. His visual acuity was counting fingers at 3 ft (1 m) in the right eye and 20/40 in the left eye. Slit-lamp examination revealed cortical opacities and nuclear sclerosis in the right eye. The anterior chamber was deep in both eyes. The intraocular pressure was 18 mmHg, OU.

On 11 April 1975 the patient underwent an uncomplicated lens extraction with instillation of alpha-chymotrypsin prior to the delivery of the lens. A sprocket-type Federov iris-fixation lens was implanted and a single peripheral iridectomy was made at the 1 o'clock position. Acetylcholine chloride was injected into the anterior chamber during the final positioning of the lens. Eight 8–0 virgin silk sutures were used to close the 2-planed limbal section.

On the first postoperative day the patient was started on pilocarpine 4% q.i.d. One day later the intraocular pressure was recorded at 70 mmHg, and the anterior chamber was considered to be shallow. The peripheral iridectomy could not be visualised because of the conjunctival flap. For 16 hours an unsuccessful attempt was made to control the elevated intraocular pressure with oral acetazolamide and intravenous mannitol.

It was then elected to perform a second surgical procedure. Fluid vitreous was aspirated through the original incision and a second peripheral iridectomy was made at 11 o'clock. Following this procedure acetazolamide was discontinued and 4% pilocarpine was given once a day for 2 days. On the fourth postoperative day the intraocular pressure was 18 mmHg. The anterior chamber was deep and the lens was in good position. By October 1975 the intraocular pressure was 11 mmHg, with the patient on no medication. The best corrected visual acuity in the right eye was 20/30.

CASE 3

A 76-year-old Caucasian female was admitted to hospital on 27 August 1975 for a cataract extraction. Visual acuity was hand motion in the right eye and 20/40 in the left eye. The right eye had a mature cataract. Intraocular pressure was 16 mmHg, OU.

On 28 August 1975 a right cataract extraction was performed through a 2-planed 160° limbal incision. Alpha-chymotrypsin was used. While the lens was being removed the posterior capsule ruptured and a small amount of liquid cortical material spilled into the anterior chamber. All remnants of cortical and capsular material were removed. During the insertion of a Worst medallion iris-fixation lens a leg of the lens was inadvertently hooked with the iris suture, and to correct this the lens was removed. At this point vitreous entered the anterior chamber and an anterior vitrectomy was done using cellulose sponges and scissors. When the anterior chamber was free of formed vitreous, the lens was repositioned and a peripheral iridectomy was made at the 12.30 position. Acetylcholine chloride was injected into the anterior chamber to constrict the pupil and re-form the anterior chamber. The section was closed with a running 10–0 nylon suture placed in a 'shoelace' fashion.

On the first postoperative day epithelial oedema, striate keratopathy, a shallow anterior chamber, and an intraocular pressure of 50 mmHg were found. The lens was in good position. Despite oral acetazolamide, betamethasone ophthalmic drops, and frequent hyperosmotic diuretics, the intraocular pressure remained elevated above 32 mmHg for 3 days. Gonioscopy revealed a closed angle inferiorly. Superiorly the iridectomy and angle were obscured by the epithelial oedema. On the fourth day the pupil was dilated with tropicamide 1% and phenylephrine 10%, every 3 hours. The lens moved superiorly, but its legs remained posterior to the iris. After 12 hours of this therapy the intraocular pressure had fallen to the high 20s, and within 24 hours the pressure was 17 mmHg, OU. Acetazolamide was discontinued, and 24 hours later the intraocular pressure was 16 mmHg. In September 1976 the visual acuity was 20/50 and the intraocular pressure was 18 mmHg, with the patient on no therapy.

CASE 4

A 64-year-old Caucasian female was admitted to hospital on 28 October 1975 for cataract extraction. The best corrected visual acuity was 20/70 in the right eye, 20/200 in the left. Intraocular pressure was 15 mmHg, OD, 18 mmHg, OS. Posterior subcapsular and anterior subcapsular opacities were noted, OU.

The patient underwent a left intracapsular cataract extraction the following day. Alpha-chymotrypsin was used. Formed vitreous was lost and 2·5 ml of fluid vitreous was aspirated through the surgical wound. A Worst medallion lens was inserted and secured to the iris with a 10–0 nylon suture. At this point a single peripheral iridectomy was made. The anterior chamber was re-formed with acetylcholine and the 2-planed incision closed with a running 10–0 nylon suture. After closure 40 mg of methylprednisolone acetate was injected subconjunctivally.

On the first postoperative day a moderate amount of epithelial oedema was noted. The lens was in good position and the anterior chamber was deep. Acetazolamide 125 mg by mouth 6-hourly was initiated. The intraocular pressure was not recorded. Nevertheless, by the third postoperative day the intraocular pressure was 42 mmHg and the anterior chamber appeared shallow. The acetazolamide was increased to 250 mg by mouth 6-hourly. 24 hours later the intraocular pressure was 50 mmHg and the iris was touching the cornea inferiorly. At this point phenylephrine 10% was given for 1 dose. The anterior chamber deepened but the pressure remained in the 40s. Intravenous mannitol was added, with no significant change in the intraocular pressure. On the fifth postoperative day, the anterior chamber remained shallow and the intraocular pressure remained elevated.

A second course of phenylephrine 10% was initiated. Following its instillation the anterior chamber deepened but the intraocular pressure remained unaltered. One dose of pilocarpine 4% was tried, but to no avail. The miotic was discontinued shortly thereafter and the patient placed on phenylephrine 10% and homatropine 5%, every 2 to 3 hours. On the sixth postoperative day the intraocular pressure fell to the low 20s, and the patient was discharged 24 hours later on phenylephrine 10%, tropicamide 1%, and homatropine 5%, every 3 hours throughout the day. In November 1976 the visual acuity was 20/50, the intraocular pressure 24 mmHg, and the patient off all medication.

Discussion

The history of intraocular lenses has been associated with pseudophakic pupillary-block glaucoma. The first intraocular lens was a posterior chamber lens, introduced by Ridley. It was placed in the posterior chamber after extracapsular cataract extraction, and this frequently resulted in a marked inflammatory response. At this point a pupillary membrane could form, obstructing normal aqueous flow and thus resulting in pupillary-block glaucoma. As described by Reese (1960) and Ridley (1964), the treatment was discission of the membrane, that is, corepraxia.

Anterior chamber lenses became popularised after the posterior chamber lenses. Here again inflammation or haemorrhage could create an obstruction to aqueous flow. This problem was discussed by Boberg-Ans (1961), Barraquer (1962), and Bresnick (1969). Another mechanism of pupillary block is the closure of the peripheral iridectomy by the supporting arms of the lens. Boberg-Ans (1961) suggested making fenestrations in the haptic support portion of the lens to prevent this.

At our institution only iris-fixation lenses have been used. The incidence of pupillary-block glaucoma with iris-supported lenses has been well documented. Nordlohne (1975) reviewed his own cases as well as those of Binkhorst and Worst. In all the cases reported by these authors, except for 1, the pupillary block occurred between the first and fourth postoperative days. Worst reported 1 case occurring 2 months after surgery. The incidence varied among surgeons. Binkhorst reported 2 cases in 534 operations (0·29%); Worst had 3 cases in 568 operations (0·45%); and Nordlohne had 5 cases in 73 operations (6·94%). In our series we had 4 cases in 106 operations for an incidence of 3·8%.

Iris-fixation lenses and iridocapsular lenses are of primary importance when considering pupillary-block glaucoma, for they are located in close proximity to the pupil along the normal route of aqueous flow. Iris-fixation lenses are usually implanted after intracapsular cataract extraction. Iridocapsular lenses are implanted after extracapsular cataract extraction and depend upon an inflammatory response between iris, lens, and posterior capsule to provide firm adhesions for stabilisation and support. With either type of lens, haemorrhage and/or inflammation enhance the possibility of obstructing the pupil.

Immediate postoperative mydriatics are not used with either lens, but in some cases miotics are used. This, too, can add to the potential for pupillary block. Regardless of the mechanism, once the pupillary pathway for aqueous is impaired, the patency of the peripheral iridectomy becomes of paramount importance. It can, however, be obstructed by blood, vitreous, lens material, trapped air, or by pigment epithelium from an incomplete iridectomy.

The diagnosis of pupillary block can easily be made, but it is frequently missed. There are several factors that should lead the surgeon to the correct diagnosis. It is usually the first postoperative complication, occurring within 48 hours of surgery. The patient frequently complains of ocular pain, disproportionate to the amount of surgical trauma. There is epithelial oedema and striate keratopathy. The anterior chamber is shallow, with iris bombé, and if an air bubble is present in the anterior chamber, it will be flattened against the back of the cornea. The intraocular pressure is elevated, usually above 40 mmHg. There is often a history of operative difficulties, such as rupture of the anterior vitreous face, with or without vitreous loss, operative hyphema, and unexpected extracapsular extraction.

The elevated intraocular pressure is usually ascribed to postoperative inflammation and/or the use of alpha-chymotrypsin. Topical steroids, carbonic anhydrase inhibitors, and hyperosmotic agents are administered, but the pathophysiological mechanisms persist and the pressure remains uncontrolled. The presence of a shallow anterior chamber may occur as a result of a wound leak, but when associated with elevated intraocular pressure, it generally implies pupillary block. In rare clinical situations, 'ciliary block' glaucoma due to ciliovitreal adhesions, as described by Weiss (1972), may underlie the problem and present in a similar manner. This diagnosis is generally made after peripheral iridectomy fails to reverse the glaucomatous situation.

Once the diagnosis is made, the treatment of pseudophakic pupillary block is relatively simple. Nordlohne (1975) outlines a 3-step approach to this complication. If the mechanism is from an air-bubble block of the peripheral iridectomy, the patient should be repositioned and the air bubble may be displaced, establishing normal flow of aqueous. If this fails, miotics should be discontinued and mydriatics administered. It should also be emphasised that mydriatic agents be used simultaneously with carbonic anhydrase inhibitors and/or hyperosmotic agents. As a third step, an additional peripheral iridectomy or transfixation of the iris should be performed.

Tessler (1975) has described the conversion of an incomplete iridectomy to a through-and-through opening with the argon laser. Perkins (1973) has reported iridotomy with a ruby laser. We have not used the laser, but its use should be considered prior to surgical reintervention.

In our series the following errors were made in diagnosis and therapy. In case 1 mydriatics were not started until 7 days postoperatively, and only after a vitreous aspiration was attempted. In case 2 the first treatment was a vitreous aspiration with a peripheral iridectomy. Mydriatics were not tried. In case 3 it took 3 days before the correct diagnosis was made and appropriate therapy begun. In case 4 the diagnosis was delayed by 1 day, and then the correct treatment was not started until 24 hours had passed. Other authors have had similar difficulties. Of the 10 cases reviewed by Nordlohne (1975) only 5 were managed following the treatment outlined in his text. In these cases surgical treatment was performed before complete medical therapy had been tried.

Even when the diagnosis of pupillary block is entertained, a fear of lens dislocation may delay the use of mydriatics. The use of an iris suture or platinum clip lens helps to mitigate this anxiety. Either from fear of dislocation or from not appreciating the potential benefits of mydriasis many surgeons at this point go directly to the next step in treatment, which is another peripheral iridectomy. In many instances unnecessary surgery can be avoided. Confusion may arise after the mydriatics are used and the anterior chamber deepens, for at this point the intraocular pressure may remain elevated for another 24 hours (cases 3 and 4). With a deep chamber one must persist with mydriatics.

Steps may be taken at the time of surgery to avoid pupillary-block glaucoma. Boberg-Ans (1965) recommends 2 peripheral iridotomies. Nordlohne (1975) suggests that they not be made too peripheral because they then become more easily blocked. If miotics are required (case 2), weak ones should be used. We also feel (cases 3 and 4) that intraocular lenses should not be implanted in eyes where excessive postoperative inflammation from an extracapsular cataract extraction is anticipated; in cases of vitreous loss; and in eyes that develop large hyphemas at the time of surgery. The use of an iris-fixation suture or an iris clip lens will prevent dislocation when mydriatics are used. The surgeon will treat the complication earlier with mydriasis if he is confident that the lens is held securely by one of these additional supports.

We thank Drs D. Boyaner and M. Kwitko for referring their cases to us.

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Effect of topical atenolol on intraocular pressure

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SUMMARY Placebo and topical atenolol (Tenormin), a selective β_1-adrenergic blocking substance with no intrinsic sympathomimetic or membrane-stabilising properties, were tested in 16 patients with ocular hypertension in a double-blind cross-over trial. Three different concentrations of atenolol (1, 2, and 4%) were investigated. After a single instillation there was a statistically significant fall in mean intraocular pressure (IOP) with all the concentrations after one hour, with a maximum after two to three hours. The effect had passed off after seven hours. In multiple-dose studies with applications three times a day for seven days there was a statistically significant fall in the mean IOP on the first day of treatment (all three concentrations), which persisted throughout the week. In the single-dose study only a slight dose-dependence was observed. This could not be confirmed in the multiple-dose trial. Pupil size, corneal sensitivity, systemic blood pressure, and heart rate were unaffected. No side effects were noted. Thus topically applied atenolol lowers IOP in patients with ocular hypertension and may be clinically useful.

Propranolol, a β-adrenergic blocking agent which inhibits both β_1 receptors (cardiac receptors) and β_2 receptors (broncho- and vasodilatating receptors), has an ocular hypotensive action when given systemically (Phillips *et al.*, 1967; Coté and Drance, 1968; Vale and Phillips, 1970; Öhrström, 1973; Pandolfi and Öhrström, 1974; Sharaf *et al.*, 1974; Wettrell and Pandolfi, 1975; Borthne, 1976; Wettrell and Pandolfi, 1976; Wettrell *et al.*, 1977). Practolol (a selective β_1 antagonist but with some intrinsic sympathomimetic activity) acts in the same way (Hagedorn and Tjoa, 1974; Wettrell and Pandolfi, 1975; Wettrell *et al.*, 1977). A fall in ocular tension has also been reported after topical application of propranolol and practolol (Musini *et al.*, 1971; Bietti, 1972; Vale *et al.*, 1972; Vale and Phillips, 1973). The mode of action is unknown but in the case of propranolol has been ascribed to secondary effects such as membrane stabilisation (Musini *et al.*, 1971).

Recently another beta-blocking compound, atenolol (Tenormin) (Fig. 1), a selective inhibitor of β_1 receptors, has been introduced. Unlike practolol and propranolol it has neither intrinsic activity nor membrane-stabilising properties (Barrett *et al.*, 1973), but when given by mouth it lowers intraocular pressure (IOP) (Elliot *et al.*, 1975; Wettrell and Pandolfi, 1975; Wettrell *et al.*, 1977). There have been no re-

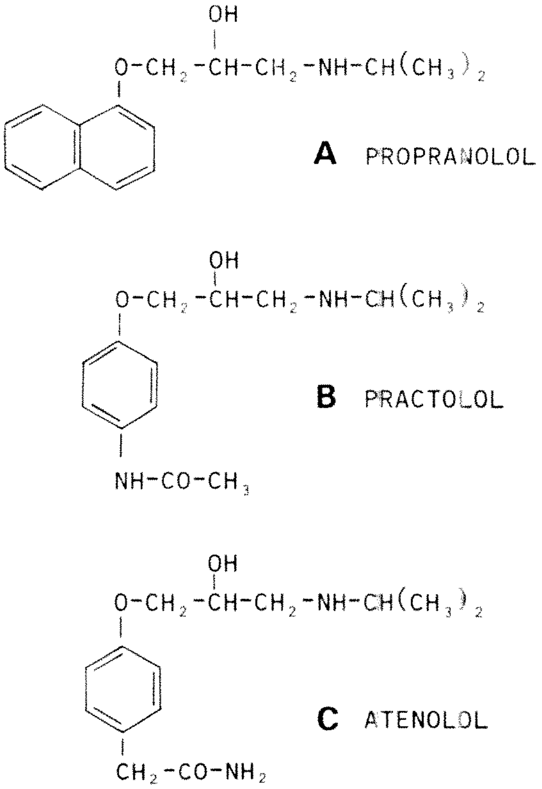

Fig. 1 *Structural formulae of beta-adrenergic inhibitors propranolol, practolol, atenolol*

Address for reprints: Karin Wettrell, MD, Department of Ophthalmology, Hospital of Malmö, University of Lund, 214 01 Malmö, Sweden ports on the local use of atenolol, and the aim of the present study was to elucidate if topically administered atenolol could reduce IOP in man, and, if so, to investigate the time-course and dose-response relationship.

Patients and drugs

The clinical material consisted of 16 patients (11 females and 5 males) of various ages (mean age 61, range 32 to 73). The subjects had an IOP $\geqslant$22 mmHg but normal visual fields and optic discs. One fellow eye in the single dose study had an untreated IOP of about 20 mmHg but was included in the trial. Some of the patients (11) were previously treated with pilocarpine, which was withdrawn at least 48 hours prior to the study. One patient did not complete the last treatment period. The subjects were not receiving systemic adrenergic drugs during the study. There was no history of asthma, bronchospasm, or other disorders contraindicating treatment with adrenergic beta-blockers. Before the study began a cardiovascular examination was made and ECG taken to ascertain suitability for the trial.

The eyedrops were prepared by ICI Pharmaceuticals and contained atenolol in concentrations 1, 2, and 4% respectively. Benzalkonium chloride (0·02% v/v) was used as a preservative and the pH was adjusted to 6·0. The placebo eyedrop had the same composition except for the absence of atenolol.

Methods

The trial was performed in a double-blind cross-over manner in which each person received the three concentrations of atenolol and placebo. The order of administration of the formulations was randomised and each concentration was tested with a drug-free interval of at least 48 hours.

Single-dose study

Eight patients (16 eyes) participated in the trial. One hour before and 0·5, 1, 1·5, 2, 3, 4, and 7 h after instillation of one drop of atenolol or placebo in both eyes IOP, pupil size, systemic blood pressure, and heart rate were recorded. IOP was measured with a Goldmann applanation tonometer, which was calibrated daily. Before tonometry 1 to 2 drops of Fluress (Pharmacia AB, Uppsala, Sweden), a combination of oxibuprocaine hydrochloride and sodium fluorescein, were instilled into the conjunctival sac. The diameter of the pupil was measured in the Goldmann perimeter, while blood pressure and heart rate were recorded after five minutes' rest in the supine position.

Multiple-dose study

Ten patients (20 eyes) were selected for the study. Two of them (one male and one female) also took part in the single-dose study. Each patient was instructed to instil 1 to 2 drops atenolol or placebo in both eyes three times daily at 7 a.m., noon, and 7 p.m. for seven days. Before the trial the baseline IOP was measured with a Goldmann applanation tonometer at 8 a.m., noon, and 4 p.m. At noon the systemic blood pressure and heart rate were measured in the supine position. Corneal sensitivity was tested with Cochet and Bonnet's aesthesiometer (Cochet and Bonnet, 1960). These measurements were repeated on the first, fourth, and seventh day of treatment. On the seventh day IOP was also recorded at 8 a.m. and 4 p.m.

Statistical analysis of the results was made by Student's *t* test for paired data. IOP during treatment with active substance and placebo were compared.

Results

One hour after the instillation of atenolol a statistically significant fall in mean IOP was observed with all the concentrations tested. This fall was maximum after two to three hours and had disappeared after seven hours (Table 1, Fig. 2). The mean maximum fall after application of 1, 2, and 4% atenolol was

Table 1 *Mean (±SEM) variation in IOP (mmHg) at intervals during a seven-hour period after a single instillation of different concentrations of atenolol compared with results with placebo (see Fig. 2). Statistical significances in parentheses*

Atenolol concentration (%)	*No. of eyes*	*Mean IOP variation (±SEM) at hour:*						
		0·5	*1·0*	*1·5*	*2·0*	*3·0*	*4·0*	*7·0*
1	16	1·1 ±0·42 (P<0·02)	−3·1 ±1·20 (P<0·05)	−3·9 ±1·29 (P<0·01)	−4·0 ±0·85 (P<0·001)	−4·9 ±0·95 (P<0·001)	−3·4 ±1·21 (P<0·02)	−0·3 ±0·62 (NS)
2	16	−0·4 ±0·91 (NS)	−3·7 ±0·71 (P<0·001)	−5·1 ±0·66 (P<0·001)	−6·1 ±0·89 (P<0·001)	−5·9 ±0·79 (P<0·001)	−4·6 ±0·94 (P<0·001)	−0·2 ±0·81 (NS)
4	16	0 (NS)	−4·9 ±0·81 (P<0·001)	−6·0 ±1·00 (P<0·001)	−6·3 ±0·88 (P<0·001)	−6·3 ±0·76 (P<0·001)	−5·7 ±1·04 (P<0·001)	−0·7 ±0·93 (NS)

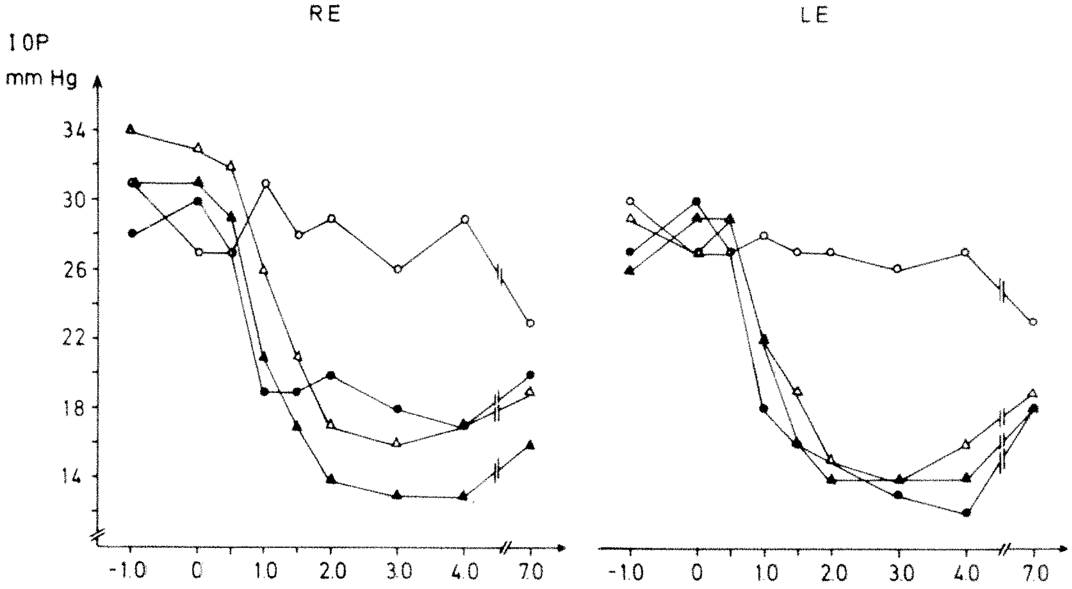

Fig. 2 *Duration of IOP response of one patient after treatment with placebo and different concentrations of atenolol. The formulations were administered at T=0 hour. Placebo (○——○). Atenolol 1% (●——●), 2% (△——△), 4% (▲——▲). RE = right eye, LE = left eye*

4·9, 6·1, and 6·3 mmHg respectively. Only a slight dose-dependence was noted.

No changes in pupil size, systemic blood pressure, or heart rate were apparent.

On the first day of treatment there was a distinct, statistically significant fall in mean IOP at noon with all concentrations of atenolol (Table 2). The mean fall was 2·4, 2·6, and 3·4 mmHg for 1, 2, and 4% concentrations respectively. The fall persisted and was statistically significant throughout the week, although the response tended to diminish at the end of the period (Table 2). The fall did not seem to be dose-dependent. A slight placebo effect was noted (Table 3, Fig. 4). Corneal sensitivity, systemic blood pressure, and heart rate were unaffected. The patients did not report any local or general side effects, and there were no signs of intolerance to the drug.

Discussion

This study shows that atenolol lowers IOP when applied topically in patients with ocular hypertension, as others have previously reported that it does when taken by mouth (Elliot *et al.*, 1975; Wettrell and Pandolfi, 1975; Wettrell *et al.*, 1977). Elliot *et al.* (1975) reported that IOP fell one hour after a single oral dose of 50 mg atenolol with a maximum fall after five hours.

We found that IOP fell one hour after topical application of atenolol and that the fall reached a

Table 2 *Mean (±SEM) variation in IOP (mmHg) at noon on days 1, 4, and 7 of one week's treatment with atenolol in different concentrations compared with results with placebo (Fig. 3)*

Atenolol concentration (%)	*No. of eyes*	*Mean IOP variation (±SEM) on day:*		
		1	*4*	*7*
1	20	−2·4±0·64 (P<0·01)	−3·0±0·66 (P<0·001)	−1·7±0·64 (P<0·02)
2	20	−2·6±0·51 (P<0·001)	−1·8±0·66 (P<0·02)	−2·0±0·29 (P<0·001)
4	18	−3·4±0·63 (P<0·001)	−3·5±0·79* (P<0·001)	−2·1±0·35 (P<0·001)

*16 eyes

Table 3 *Mean (±SEM) IOP (mmHg) after 7 days' treatment with placebo and atenolol in different concentrations (active substance compared with placebo)*

	No. of eyes	*IOP (±SEM) at:*		
		8 am	*Noon*	*4 pm*
Untreated	20	25·9±0·80	24·0±0·61	23·0±0·73
Placebo	20	24·9±0·87	22·8±0·66 (P<0·05)	22·1±0·77
1% Atenolol	20	22·2±0·60 (P<0·01)	21·2±0·88 (P<0·05)	20·7±0·56
2% Atenolol	20	22·4±0·57 (P<0·001)	20·8±0·54 (P<0·001)	21·4±0·73
4% Atenolol	18	23·3±0·76 (P<0·05)	20·6±0·50 (P<0·001)	20·8±0·61 (P<0·01)

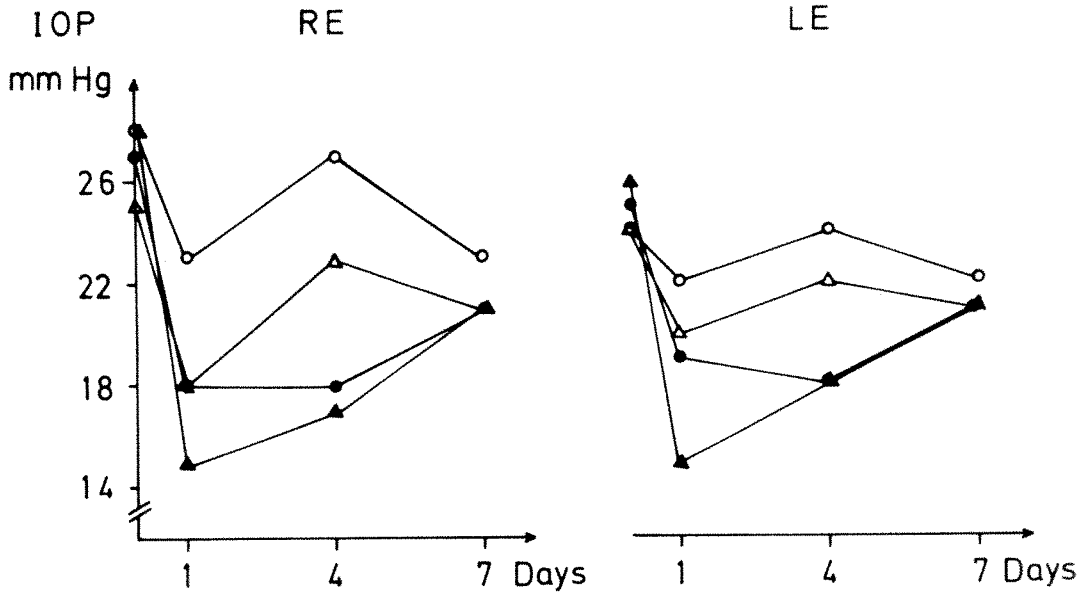

Fig. 3 *IOP in one patient during seven days' treatment with placebo and different concentrations of atenolol three times daily. Placebo* (○——○). *Atenolol 1%* (●——●), *2%* (△——△), *4%* (▲——▲)

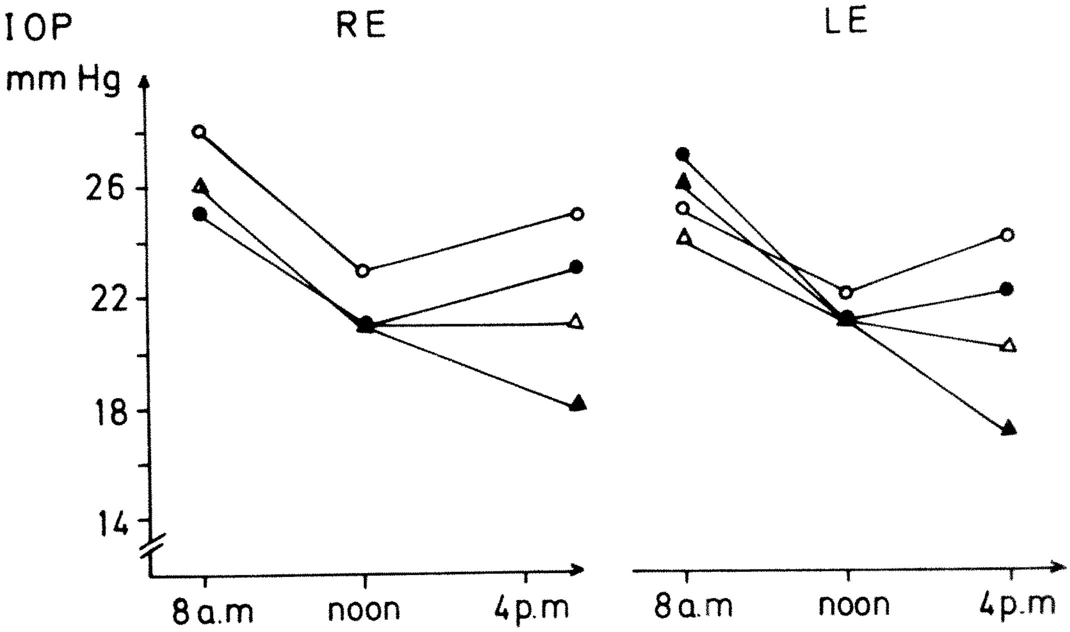

Fig. 4 *Diurnal IOP in one patient after seven days' treatment with placebo and different concentrations of atenolol three times daily. Placebo* (○——○). *Atenolol 1%* (●——●), *2%* (△——△), *4%* (▲——▲)

maximum after two to three hours. A similar time course has been described with other topically administered β antagonists such as propranolol, practolol, pindolol, and oxprenolol (Vale *et al.*, 1972; Vale and Phillips, 1973; Bonomi and Steindler, 1975; Bucci, 1976), but these substances have caused side effects such as hyperaemia of the conjunctiva and discomfort.

Unlike propranolol, atenolol has no membrane stabilising properties. Thus it had no effect on corneal sensitivity in our patients. This disproves the assumption that it is the anaesthetic action that causes the fall in IOP (Musini *et al.*, 1971). Its lack of anaesthetic properties and the absence of adverse reactions seem to make atenolol more suitable for local application than other beta-blockers. Atenolol is a selective β_1 antagonist without intrinsic activity. This suggests that its action in reducing IOP must in some way be mediated by the inhibition of the β_1 receptors in the eye. It remains to be seen whether this inhibition causes an increase in outflow facility or impairs the production of aqueous humour.

In our multiple-dose study the fall in IOP was less than the maximum effect in the single-dose trial. Nevertheless, in the multiple-dose study IOP was measured at noon—that is, about five hours after the first application of atenolol and immediately before the second application. Therefore, judging from the single-dose study, the maximum effect had already passed and the IOP was recorded in the recovery phase.

In the multiple-dose study a tendency to tachyphylaxis to the drug was observed at the end of the treatment. This diminished drug response was more pronounced in the diurnal measurements of IOP on the same day. Similar phenomena have been described after treatment with adrenergic substances such as salbutamol and epinephrine (Paterson and Paterson, 1971, 1972; Langham, 1974; Langham and Diggs, 1974; Langham, 1975).

Our study seems to justify further investigation to ascertain whether local treatment with atenolol has a place in the treatment of glaucoma.

We thank Miss Ulla Andersson for technical assistance. The study was supported by grants from the Swedish Society of Medical Sciences and the Medical Faculty of Lund University. Atenolol was kindly supplied by ICI-Pharma, Gothenburg, Sweden.

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British Journal of Ophthalmology, 1977, **61**, 339–344

Reticulin fibres in relation to retinal vessels

AMJAD RAHI AND NORMAN ASHTON

From the Department of Pathology, Institute of Ophthalmology, University of London

SUMMARY Argyrophilic perivascular and intervascular fibres in the mammalian retina are shown by specific antireticulin immunofluorescence to consist of reticulin. The possible significance of these findings is briefly discussed.

Some recent studies in the retina of man and animals have reported the presence of perivascular and intervascular fibres which, by reason of their argyrophilia, ultrastructure, and enzymatic digestion were believed to consist of reticulin (Daicker, 1971a, b; Ashton and Tripathi, 1975). The latter authors, however, pointed out the unreliability of these criteria and suggested that the problem might be resolved by the use of specific immunofluorescent staining of reticulin.

An immunohistochemical method for demonstrating reticulin fibres in tissues has recently been described (Seah *et al.*, 1971). Human sera containing reticulin antibodies were found to stain reticulin fibres in the rat liver, stomach, and kidney, and the patterns resembled very closely the silver impregnation staining technique. The immunofluorescence was not impaired, and was even enhanced by pretreatment with collagenase but was abolished by periodate, and the authors were convinced that the fibres were in fact reticulin. Moreover, a considerable advance was made by Pras and Glynn (1973), who recently extracted from reticulin by a water dispersion method a noncollagenous protein, the antibodies of which showed specific antireticulin activity by immunofluorescent techniques. We have employed both these methods of investigation in the retinas of monkeys and rats and now report our findings.

Material and methods

RETICULIN ANTISERA

The specific antisera used in the present study were obtained from patients suffering from either uveitis or coeliac disease, conditions known to be associated with the presence of antireticulin antibodies (Seah *et al.*, 1971; Rahi *et al.*, 1976) or else prepared in this laboratory in New Zealand albino rabbits according to the following schedule: 4 mg of a noncollagenous component of reticulin protein prepared according to the method of Pras and Glynn (1973)*, was ultrasonically dispersed in 2 ml of distilled water, and emulsified in equal volumes of Freund's complete adjuvant and injected intramuscularly into the animals at 4 different sites. The injection was repeated twice at 2 weeks and 4 weeks after the initial dose, and the animal was bled 1 week after the last injection. The serum was stored in aliquots at −20°C.

IMMUNOFLUORESCENCE TEST

Frozen sections of a composite block consisting of the liver, kidney, diaphragm, and stomach of a rat were used to test the specificity of the antisera. Frozen sections of eyes from rats and monkeys and capillaries isolated from rat retinas by the acid water technique were stained to demonstrate the perivascular and intervascular reticular fibres. A standard indirect immunofluorescent staining technique was used. Fluorescein labelled antihuman and antirabbit immunoglobulins were obtained from the Wellcome Laboratories. A Zeiss epifluorescence microscope equipped with a fluorescein isothiocyanate (FITC) interference filter was used to examine the stained sections.

Findings

The reticulin antisera obtained from patients and from immunised rabbits gave typical staining patterns (Rizzetto and Doniach, 1973; Williamson *et al.*, 1976) in the liver, kidney, and stomach (Figs. 1, 2, and 3). The septal fibres within the connective tissue of the optic nerve stained intensely (Fig. 4).

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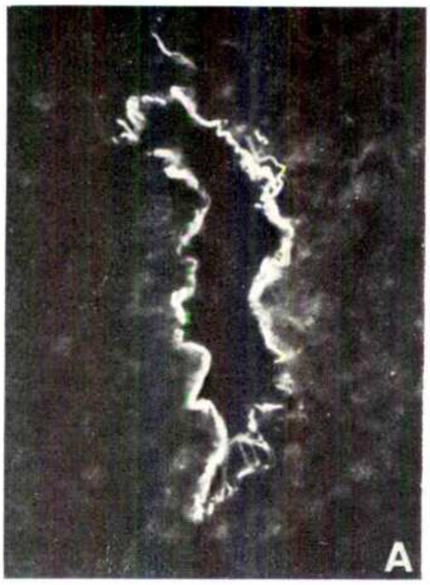
*This extract was kindly provided by Dr L. E. Glynn, director of the Mathilda and Terence Kennedy Institute of Rheumatology, London



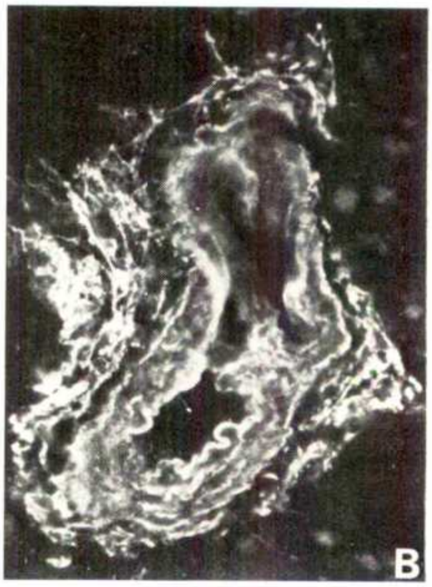


Fig. 1 *Indirect immunofluorescence test on rat liver. The antireticulin serum reacts with the reticulin fibres in the central portal vein* (A) *and the branches of hepatic artery* (B) *to produce a bright fluorescence. Unfixed cryostat section* × 360

In the sections of the retina fluorescent staining was confined to the perivascular fibres and also outlined the vascular endothelium (Figs. 5, 6, 7, and 8). Isolated rat retinal vessels showed coarse longitudinal and branching fluorescent networks of perivascular fibres (Fig. 9). These appearances exactly corresponded to those demonstrated in silver-stained preparations (Ashton and Tripathi, 1975) and established the reticulin nature of these fibres (Fig. 10).

Discussion

The fact that reticulin exists in the retina in the form of perivascular networks and intercapillary strands and bridges is of academic interest and of pathological significance. There has for many years been controversy as to the biochemical nature of reticulin fibres and hesitancy in correlating their microscopical and ultrastructural properties, to the extent that the term 'reticulin' is generally avoided

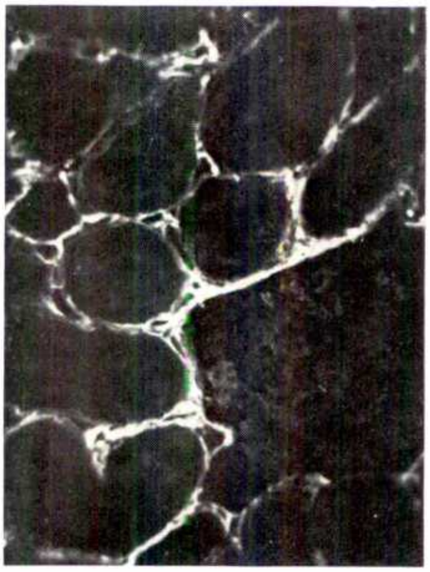


Fig. 2 (left) *Peritubular reticulin fluorescence in a rat kidney demonstrated by the same technique as in Fig. 1* × 360

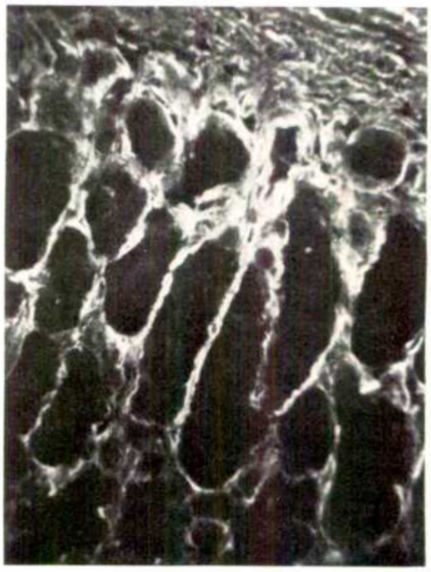


Fig. 3 (right) *Periglandular reticulin fluorescence in a rat stomach demonstrated by the same technique as Fig. 1* × 270

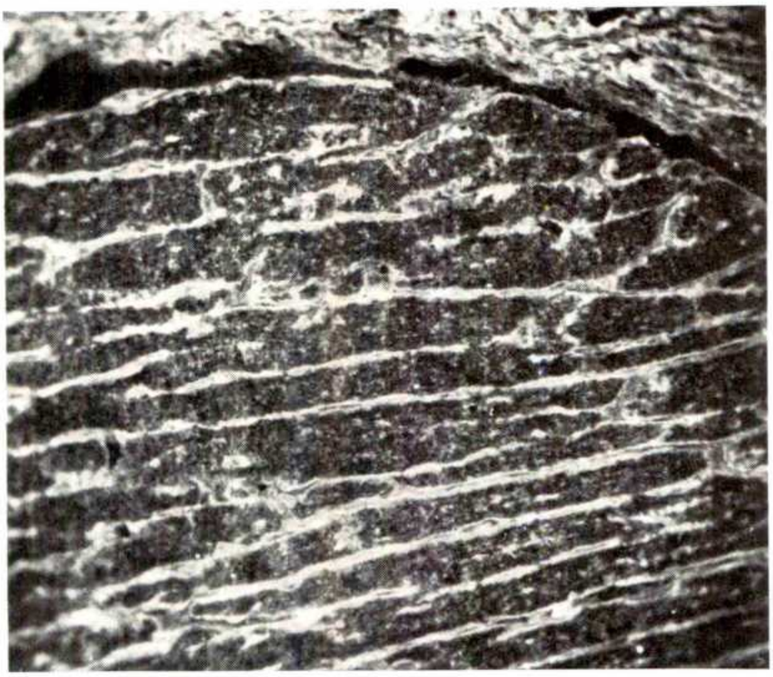


Fig. 4 *The septal reticulin fibres in the optic nerve of a monkey show bright fluorescence when treated with specific antiserum. Unfixed cryostat section* ×175

by electron microscopists. Cervos-Navarro and Matakas (1975) claim that they were the first to describe the ultrastructure of reticulin in 1972 (Matakas and Cervos-Navarro, 1972). In view of the close anatomical relationship between basement membrane and reticulin, described in the retina by Ashton and Tripathi (1975), it is noteworthy that Cervos-Navarro and Matakas (1975) consider that

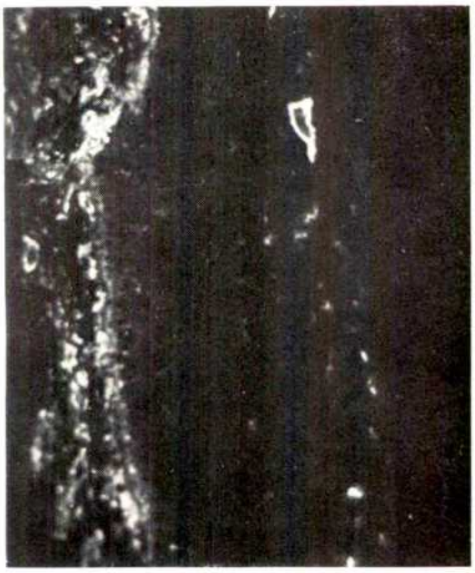


Fig. 5 *Cross-section of rat retina treated with antireticulin serum. Bright perivascular fluorescence was seen in the retinal vessels* (right) *and in the choroidal vessels* (left). *Indirect immunofluorescence test. Unfixed cryostat section* ×360

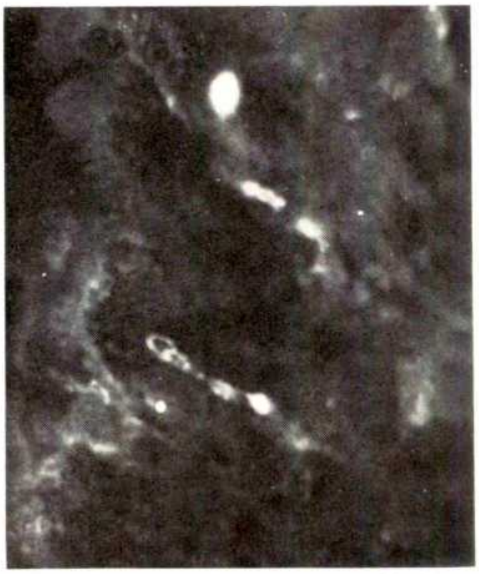


Fig. 6 *Flat section of rat retina treated by the same technique as in Fig. 5. Bright fluorescence is present within the capillary walls* ×360

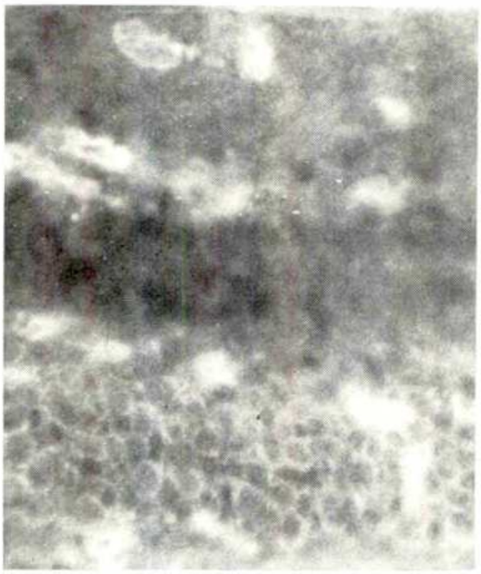


Fig. 7 *Positive fluorescence of reticulin fibres in the capillaries of the monkey retina (cross-section) seen partially in focus in a thick unfixed cryostat section* ×360

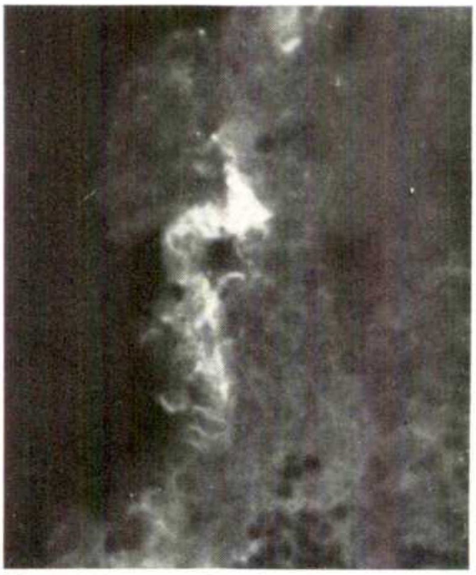


Fig. 8 *Flat section of monkey retina showing fluorescence in a pericapillary reticulin network with strands extending into retina. Unfixed cryostat section* ×480

basement membrane is the substrate of reticulin, a correspondence first mentioned by Robb-Smith (1970). They emphasise that the fibrillar form of reticulin seems to be only a light-microscopical finding and possibly caused by formalin fixation in some instances. In the present study, however, we have demonstrated them by immunofluorescence in unfixed frozen sections; nevertheless, perivascular reticulin networks are certainly more readily demonstrated by silver staining in formalin fixed tissue.

The reticular fibres in the retinal vessels stained less brilliantly than those in the optic nerve, the liver, the kidneys, and the stomach. As the product of immunofluorescence, like any other chemical reaction, is generally directly proportional to the concentration of the reactants, this weak staining may be due to a relatively smaller amount of these fibres in the retina than in other tissues.

Since reticulin appears to exist in several different morphological (Vizioli *et al.*, 1974) and immuno-

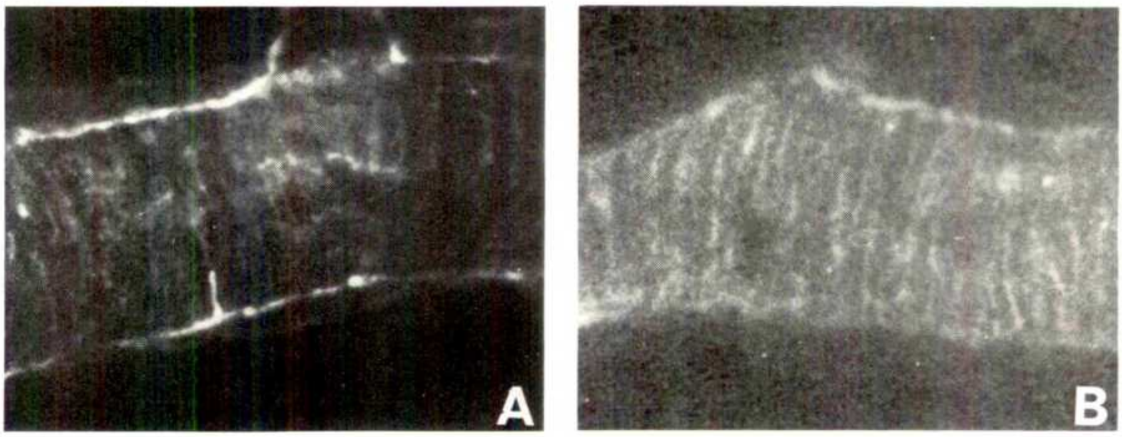


Fig. 9 (A *and* B) *Rat retina. Capillaries isolated by acid-water techniques show fluorescent networks around capillaries treated with specific antiserum. Unfixed* ×1000

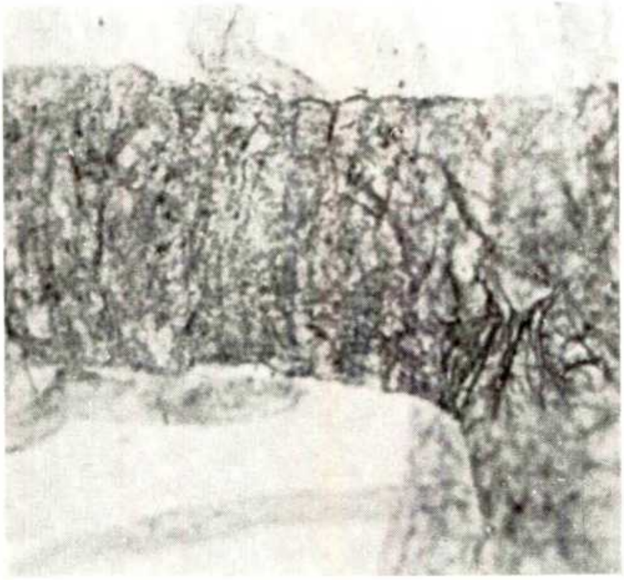


Fig. 10 *Retinal capillary from same retina as in Fig. 9 but post-fixed in formalin and stained by the Gomori method for reticulin. The fluorescent fibres now appear argyrophilic and show the typical network. The silver is probably deposited on the antigenic glycoprotein component of the reticulin* ×1000

logical forms (Rizzetto and Doniach, 1973; Boyd *et al.*, 1976), it is possible that the antiserum which we used in the present study was not strong enough to react with all the 'organ' and 'non-organ' specific reticular fibres in the retina.

There is now general agreement, however, that reticulin is a type of collagen protein rich in carbohydrate (Perez-Tamayo and Rojkind, 1973) in the form of polysaccharide side chains which effectively reduce the cross-linkage and so prevent aggregation into typical collagen fibres (Muir, 1973). It has only recently become clear that there are at least four genetically distinct types of mammalian collagen (Grant *et al.*, 1975; Rojkind and Martinez-Palomo, 1976). Type I, the conventional collagen found in cornea, skin, bone, and tendon, consists of two $\alpha 1(I)$ polypeptide chains and one $\alpha 2$ polypeptide chain. Type II, the type found in hyaline cartilage, consists of three $\alpha 1(II)$ polypeptide chains. Type III, found in small quantities in several connective tissues and in large amounts in the fetal skin and blood vessels, contains three $\alpha 1(III)$ polypeptide chains. It is now believed that reticulin fibres belong to this latter class of the collagen family but for reasons already referred to have failed to aggregate. Type IV, the fibrillar material found in basement membranes and the lens capsule, consists of three $\alpha 1(IV)$ polypeptide chains.

In previous papers the distribution of argyrophilic fibres in the normal retina has been demonstrated (Daicker, 1971; Ashton and Tripathi, 1975), and although it cannot be said that all such fibres are reticulin it is now clear that this may well be the case, but the proliferating argyrophilic fibres found in retinal disease may have a glial component. This would seem unlikely, since it was shown in electron micrographs by Ashton and Tripathi (1975) that glia remained unstained with silver methenamine in contrast to the positive staining of adjacent proliferating perivascular fibres now identified as reticulin. It would appear, therefore, that some reactions in the diseased retina previously described as gliosis are rather to be regarded as collagenous in nature. But, since fibroblasts are not usually associated with such proliferations within the retina, the cellular source of the collagenous protein, whether from endothelial cells, muscle cells, pericytes, or all three, is unclear, while the frequent replacement in degenerate and senile vascular retinopathies of basement membrane and reticulin fibres by fibres ultrastructurally indistinguishable from conventional collagen (i.e., type I) has yet to be explained.

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British Journal of Ophthalmology, 1977, **61**, 345–348

Comparison of ocular hypotensive effects of acetazolamide and atenolol

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SUMMARY The ocular hypotensive effect of single oral doses of (*a*) atenolol (50 mg), (*b*) acetazolamide (500 mg), (*c*) atenolol (50 mg) and acetazolamide (500 mg) in combination, and (*d*) vehicle (inert tablets) were compared in 8 patients with glaucoma. In this single-dose, double-masked trial the combination was observed as most effective in reducing ocular tension. Both the combination and atenolol performed markedly better than vehicle. That acetazolamide did not reduce ocular tension significantly more than vehicle is probably explained by relatively low initial ocular tensions. There was no evidence of interaction between atenolol and acetazolamide in this study. Acetazolamide probably remains the first-choice oral medication for glaucoma. It is cautiously suggested that beta-blocking drugs may have a future therapeutic role, but longer-term studies on larger numbers will be required to establish this.

The carbonic anhydrase inhibitors have been used in the therapy of the glaucomas for 20 years (Becker, 1954). It is accepted that their principal action is to reduce the production of aqueous humour, but their exact mode of action has not yet been established. Whatever their action, their effectivity has established them as the drugs most commonly given by mouth for glaucoma.

In recent years beta-adrenergic blocking drugs have been shown to reduce ocular tension in glaucoma patients both when administered systemically, as first reported by Phillips *et al.* (1967) and topically (Vale *et al.*, 1972; Bonomi and Steindler, 1975). Their ocular hypotensive effect is probably due to blockade of beta receptors and not to intrinsic sympathomimetic (beta) nor to a membrane-stabilising effect (Elliot *et al.*, 1975), though enhanced alpha activity is a possibility (Norton and Verstein, 1972). They may affect aqueous production and/or outflow, or conceivably have some other effector mechanism. In some other areas the beta-adrenergic receptor is thought to be linked to the enzyme adenyl cyclase (Jenkinson, 1973).

Accordingly it would be interesting and useful to compare the ocular hypotensive effects of a carbonic anhydrase inhibitor and a beta-blocking drug and also to ascertain whether there was any interaction between them. For this study we chose the new beta-adrenergic blocker atenolol (Tenormin, ICI), as it is free from sympathomimetic or local anaesthetic activity and has been used by us previously (Elliot *et al.*, 1975), and the carbonic anhydrase inhibitor acetazolamide (Diamox), as it is the most commonly used drug of the group.

Aims

(1) To compare the effects of single oral doses of acetazolamide (500 mg), atenolol (50 mg), and a vehicle preparation on the intraocular pressure of 8 glaucomatous patients. (2) To compare with the above the effect of a combination of atenolol 50 mg + acetazolamide 500 mg. (3) To assess whether there was any drug interaction.

Methods

1. Patients. Of the 8 patients selected, 6 had open-angle and 2 chronic closed-angle glaucoma. In all cases 1 eye only was examined; the right eye was selected unless clinically contraindicated (1 case). All had been attending the hospital for months or years and were selected because of their mobility

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and relative proximity to the hospital. Their informed consent was obtained for the investigations.

2. Measurements. The 8 subjects attended as outpatients for 4 test days, each separated by at least 1 week. Systemic carbonic anhydrase inhibitors (1 patient only) and local therapy to the test eye (all patients) were stopped 24 hours before each test day. These arrangements were made to diminish the influence on study results of non-test preparations.

On each day the ocular tension in the selected eye was measured at 09.00 hours. The tablets were then taken by mouth and the tension was measured hourly for 7 hours.

3. Design. It was recognised that the order in which patients received the 4 test drugs might influence drug response. The assumption was made that the residual effect of a previous test drug might act on the patient's response to the immediately following drug but would not influence response to later test preparations.

Patients entered the trial serially, but an attempt (not entirely successful) was made to study patients in blocks of 4, so that the 4 patients in a block received their first test preparation more or less at the same time. Within each block test drugs were assigned to patients according to a Latin square design. Besides ensuring that every patient received each test drug once and only once, this allowed residual treatment effects to be balanced and meant that on the patients' first study day exactly 1 patient from each block received each test drug, and similarly on study days 2, 3, 4. The design is illustrated in Table 1.

The trial was double-masked. An envelope was prepared by the statistician for each patient; inside were sealed individually the patient's treatment assignments for study days 1 to 4. Each 'treatment' consisted of 3 tablets (since acetazolamide + atenolol was given as 2 acetazolamide tablets each of 250 mg + 1 atenolol tablet of 50 mg), and neither patient nor tonometrist was aware of which preparation was being taken. All tablets were white and of the same size, though not identically marked.

Table 1 *Latin square design*

	Block 1				*Block 2*			
Patient study day	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
1	d	a	V	ad	V	d	a	ad
2	ad	d	a	V	a	ad	d	V
3	a	V	ad	d	ad	a	V	d
4	V	ad	d	a	d	V	ad	a

V = vehicle; a = atenolol; d = acetazolamide; ad = atenolol + acetazolamide

Table 2

Average total fall in IOP		*Comparison adjusted means*	
V	0·58	a : d	NS
a	5·49	d : V	NS
d	2·73	ad : a	NS
ad	8·82	a : V	$0·01 < P < 0·05$
		ad : V	$P < 0·01$

Table 3

Average fall in IOP during first 3 hours		*Comparison adjusted means*	
		a : d	$0·01 < P < 0·05$
V	0·10	d : V	NS
a	4·95	ad : a	$0·01 < P < 0·05$
d	1·79	a : V	$P < 0·01$
ad	8·31	ad : V	$P < 0·01$

Table 4

Average fall in IOP during last 4 hours		*Comparison adjusted means*	
		a : d	NS
V	1·08	d : V	NS
a	5·89	ad : a	NS
d	3·43	a : V	$0·01 < P < 0·05$
ad	9·21	ad : V	$P < 0·01$

Table 5

Average maximum expected fall		*Comparison adjusted means*	
		a : d	NS
V	1·46	d : V	NS
a	6·35	ad : a	NS
d	3·78	a : V	$0·01 < P < 0·05$
ad	9·40	ad : V	$P < 0·01$

V = vehicle; a = atenolol; d = acetazolamide; ad = atenolol + acetazolamide. Measurements in mmHg. Figures adjusted for residual effects. NS = not significant. P values from multiple range test.

The statistical analysis was derived from the work of Williams (1949).

Results

Underlying the study were the prior assumptions that initial ocular tension would be in the range 20 to 30 mmHg and that a reduction of about 5 mmHg could be expected on treatment. The maximum fall in ocular tension was expected 4 to 5 hours after administration of the tablets (at 13.00 to 14.00 hours).

1. Comparison of atenolol, acetazolamide, and a combination of atenolol and acetazolamide

Although Tables 2 to 5 and Fig. 1 suggest that the order of potency as ocular hypotensive agents is 50 mg acetazolamide alone, then vehicle alone, the only significant comparisons are atenolol > vehicle ($P < 0·05$) and atenolol + acetazolamide > vehicle ($P < 0·01$).

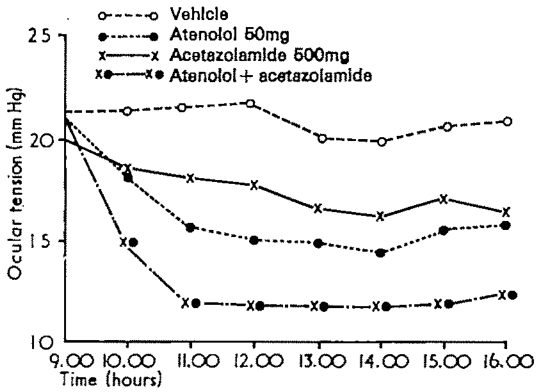

Fig. 1 *Mean pressures (8 patients) in mmHg (applanation) for each treatment plotted against time in hours. Note: This graph is the clearest way of presenting the results visually, but differences were used for the statistical analysis*

Only in the period of the first 3 hours after administration was atenolol alone more effective than acetazolamide ($P < 0{\cdot}05$) and atenolol + acetazolamide more effective than atenolol alone ($P < 0{\cdot}05$).

2. Evidence of interaction between atenolol and acetazolamide
Statistical analysis shows no evidence of any interaction. The combination of drugs is the most effective, but no extra or lesser effect is shown over the simple *addition* of the effects of the drugs singly.

3. Comparison between acetazolamide and vehicle
Although acetazolamide reduced ocular tension, surprisingly there was no statistically significant difference between its effect and that of the vehicle preparation.

Analysis

Four response variables were defined, and the results of analyses are shown in Tables 2 to 5: (1) Average fall in ocular tension throughout the day, referred to as average total fall; (2) average fall in ocular tension during first 3 hours; (3) average fall in ocular tension during last 4 hours; (4) average expected maximum fall in ocular tension—that is, difference between ocular tension at 09.00 hours and mean ocular tension at 13.00 and 14.00 hours (see Fig. 1).

Allowance was made in the analysis for patient effects and in-block study day factors. Tables 2 to 5 show mean fall under treatment after adjustment to compensate for residual treatment effect (the adjustments are in all cases minor). The standard deviation for the comparison between two adjusted treatment means is 1·56, 1·38, 1·78, 1·67 for response variables 1 to 4 respectively. The statistical significance for several comparisons between pairs of treatment means, based on the multiple range test of Duncan (1955), is noted in Tables 2 to 5.

It should be pointed out that responses by the same patient to 4 drugs are almost surely positively correlated, so that the analysis of variance described above, relying as it does on uncorrelated error terms, is likely to be conservative and may fail to detect a significant difference between treatments. As a check, therefore, a paired comparison has been made within patients of response to vehicle and acetazolamide. There is still no statistically significant difference between response to vehicle and acetazolamide. The 3 patients who responded well to acetazolamide were those with the highest initial ocular tension. The average total falls for these 3 patients were 6·0, 5·7, and 5·3 mmHg.

Interaction (+ or −) between atenolol and acetazolamide was assessed by comparison between the observed effect of the combination on ocular tension and that predicted from the sum of the observed falls in pressure produced by each drug separately.

Discussion

In this study a single oral dose of atenolol (50 mg) was more effective than acetazolamide (500 mg) in reducing ocular tension in the first 3 hours after administration of the drug by mouth. The use of the 2 drugs together in these doses produced an additive effect but no interaction—i.e., the combination neither enhances nor diminishes the individual drug effect.

It is surprising that in this single-dose study acetazolamide, although reducing ocular tension, did not do so to a significantly greater extent than a vehicle preparation. The explanation probably lies in the fact that initial ocular tensions were not very high in this series (median 20, range 16 to 30).

We think that, even if both drugs reduce production of aqueous humour, they act by a different mechanism, since there was no evidence of interaction between the two. Although in this single-dose study a beta blocker was more effective than a carbonic anhydrase inhibitor, longer trials would be required to establish whether this relative effectiveness was maintained. There is some evidence that the beta-blocking drugs *can* maintain their ocular hypotensive action (Coté and Drance, 1968; Pandolfi, 1974; Bonomi and Steindler, 1975).

Toxicity
The side-effects of carbonic anhydrase inhibitors are well known and include gastrointestinal intolerance, paraesthesiae, ureteric colic, and drug eruptions. The beta-blocking drugs have 2 main groups of side-effects. The first are due to their generalised beta-adrenergic blocking activity and include bronchospasm, precipitation of heart

failure and, in treated diabetics, slight hypoglycaemia; they lower systemic blood pressure, which is a potential disadvantage if they are used for systemic treatment of glaucoma.

Some of these reactions can be minimised by utilising drugs which are more selective in their action and by avoiding their use in 'at-risk' patients —e.g., those with a history of bronchospasm. A more serious group of toxic reactions, however, have in the past few years been described in association with the beta$_1$-blocker practolol. These have been fully discussed recently (leading article, 1975; editorial, 1976).

The non-selective beta-blocker propranolol, which has been in use for over a decade, has not been reported as being associated with the oculo-mucocutaneous syndrome (though it can, of course, cause the other generalised effects of beta-blockade indicated above). Propranolol is almost equipotent with atenolol in its ocular hypotensive effect when given orally (Macdonald *et al.*, 1976), and despite the disadvantage of having some local-anaesthetic-like activity is also effective on topical administration (Vale *et al.*, 1972).

Although the beta-blocking drugs given orally are now being used in the clinical management of the glaucomas in some centres (Pandolfi and Öhrström, 1974), acetazolamide probably remains the oral treatment of choice. In difficult selected cases supplementing treatment with a beta-blocking drug systemically would not at present appear to reduce the effectiveness of a carbonic anhydrase inhibitor; indeed, their effects are additive in this single-dose study.

Topical treatment, of course, remains the initial treatment of choice (pilocarpine, adrenaline, etc.). Preliminary trials with atenolol eye drops have given some encouraging results (Phillips *et al.*, 1976) and the need for systemic administration may be superseded.

We are grateful to ICI (Pharmaceuticals) Ltd for supplies of atenolol (Tenormin, ICI) and for a grant for expenses, and to Dr Rushton, of ICI, for helpful information and discussion.

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Atenolol eye drops in glaucoma: a double-masked, controlled study

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SUMMARY Guttae atenolol 4% (Tenormin), a pure beta$_1$-blocking (i.e., cardioselective) drug, produced a median overall fall of 5·6 mmHg (range 3·2 to 13·2 mmHg) in the first tonometrised eyes of 7 patients with open-angle glaucoma or ocular hypertension and 1 with closed-angle glaucoma (off any treatment for the whole of the day preceding each test day) after allowance for an 'effect' of guttae saline 0·9%, in a double-masked, cross-over trial. By a Wilcoxon matched pairs rank test this was significant at the $P<0·05$ level. The median overall fall of 3·5 mmHg (range 0·8 to 10·8 mmHg) in the second-tonometrised eyes of 7 patients (1 of the 8 contributed only 1 eye) was also significant ($P<0·05$).

In 2 patients who had been treated with guttae atenolol 4% daily 3× for 1 and 2 months there is evidence that, on replacing the atenolol 4% with saline 0·9%, a rise of pressure of around 3 mmHg occurred 2 and 3 and 5 days later, i.e., the drug still retained its effectivity (? slightly reduced) after 1 and 2 months.

Atenolol (Tenormin) is a recently introduced beta-adrenergic blocking drug which is cardioselective, i.e., blocks β_1 effects on the heart and lacks intrinsic sympathomimetic properties as well as membrane-stabilising effects (Barrett *et al.*, 1973). Orally, it has already been shown to reduce ocular tension (Elliot *et al.*, 1975; Wettrell and Pandolfi, 1975), as do other beta-blocking drugs.

The present trial was devised because topical treatment by drugs which reduce blood pressure seems preferable to their systemic use. There was some expectation of success because guttae propranolol 1% (Musini *et al.*, 1971; Vale *et al.*, 1972), guttae practolol 10% (Vale and Phillips, 1973), and guttae pindolol 1% (Bonomi and Steindler, 1975) are already known to reduce ocular tension. Two preliminary studies of guttae atenolol 4% on normal volunteers were made at this hospital; one showed a small but statistically significant reduction in tension (Phillips *et al.*, 1976). An important advantage of atenolol over propranolol is the absence of local anaesthetic effect and over practolol the absence of any evidence of serious toxic side-effects.

The aim was to assess whether guttae atenolol 4% instilled into both conjunctival sacs reduces ocular tension when compared with guttae saline 0·9% in a randomised double-masked trial on 8 patients.

Method

Seven patients with open-angle glaucoma or ocular hypertension and 1 with closed-angle glaucoma were entered into the study serially. They gave informed consent to the investigation, which involved all-day attendance as outpatients on the same day in 2 consecutive weeks. Details from the patients' histories are given in Table 1.

Patients were taken off treatment on the day preceding each study day. Throughout the trial, for each patient, both eyes were treated and tonometrised systematically in the order right eye first, followed by left eye unless there were clinical contraindications. This occurred in 1 patient whose right eye was his only seeing eye, so that, although both eyes were treated, only the left was tonometrised.

Reference pressure was taken at 0900 in both eyes (with the exception of the patient described above) on both days of study just prior to administration of drops. Thereafter tonometry was done at 1½, 3½, 5½, and 7½ hours after treatment.

Drops were administered by the tonometrist from a bottle identified by the patient's code number and

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Table 1 *Diagnoses and current treatment of patients*

Patient No.	*Age (in years)*	*Sex*	*Diagnosis*	*Treatment*
1	72	M	R. and L. open-angle glaucoma	Pilocarpine eye drops 4%, daily 4 ×, R. and L. Eppy eye drops 1%, daily 2 ×, R. and L.
2	64	M	R. open-angle glaucoma	Aged 60 Trephine Aged 63 Leaking bleb: conjunctival flap re-made Pilocarpine eye drops 2% each a.m. Eppy eye drops 1%, daily 2 ×
			L. ocular hypertension	Pilocarpine eye drops 4%, daily 4 × Eppy eye drops 1%, daily 2 ×
3	67	F	R. and L. open-angle glaucoma	Pilocarpine eye drops 2%, daily 3 ×, R. and L.
4	64	F	R. and L. open-angle glaucoma	Pilocarpine eye drops 1%, daily 3 ×, R. and L.
5	62	M	R. predisposed to CAG L. closed-angle glaucoma (50% closed) with central vein occlusion	R. prophylactic peripheral iridectomy 4 months ago L. sector iridectomy 4 months ago. No drops
6	68	M	R. and L. ocular hypertension	Nil
7	68	F	R. and L. ocular hypertension	Atenolol eye drops 4%, daily 4 ×, R. and L.
8	79	F	R. Ocular hypertension L. open-angle glaucoma	Nil

study day. The trial was thus double-masked, neither tonometrist nor patients being aware of treatment assignment at any time during the study.

The randomisation scheme, giving the treatment assignments for each patient, was devised to ensure that 4 of the 8 patients received guttae atenolol 4% on their first study day. The remaining 4 patients were given guttae saline 0·9%. On the second study day treatments were crossed over. The order of treatment for the first patient who entered the study was transposed, however. This patient had been assigned saline on day 1, but the bottle was empty and the tonometrist was ignorant as to which preparation had evaporated. Both to avoid inconvenience to the patient and violation of the masking, the assignment for day 2 was used. As a result of the transposition the balance of the design altered, 5 patients receiving guttae atenolol 4% as day 1 treatment instead of 4 as planned. The order in which treatments were administered does not appear to influence the magnitude of response, however, and so the departure is unlikely to be serious.

Results

Fig. 1 shows the graphs of tonometry on the first tonometrised eyes in the 8 patients (right eye for all but patient 5).

There is a consistent advantage in favour of the atenolol-treated eye compared with the saline-treated eye (median 5·6 mmHg, range 3·2 to 13·2 mmHg, $P<0{\cdot}05$, Wilcoxon matched pairs signed rank test).

Table 2 summarises the response to atenolol by first and second tonometrised eyes in the study patients.

It may be interesting to note that in 6 out of 7 patients the response to atenolol was lower in the patient's second treated than first treated eye. This observation is not statistically significant.

Discussion

Although these 1-day observations have shown a statistically significant decrease in ocular tension produced by guttae atenolol 4% when compared with guttae saline 0·9%, much more information is required before such drops should be used regularly in the treatment of glaucoma. However, so far as they go, the results are encouraging. Investigations on the following points should be done:

(a) *Duration of action.* The interval between drops was arbitrary and based on a previous study (Elliot *et al.*, 1975), which suggested a duration of action of the systemic drug of 7 hours. A separate study would be useful to elucidate time taken for the hypotensive effect to disappear (*i*) after 1 dose and (*ii*) after use of the drops for several months.

(b) *Effectivity over time.* It is quite likely that the effectivity of the drops will be greater during the first 12 hours than subsequently. We have obtained information on 2 patients in this regard. After a month on guttae atenolol 4% right and left alone, patient No. 7 was admitted to hospital on day 1, and tonometrised at 0930, 1230, 1430, and 1630 on days 2 to 5 and discharged on day 6. On day 2 she was given guttae atenolol 4% right and left at 0800, 1200, and 1600 but this was changed (unknown to the patient and tonometrist) to guttae saline 0·9% right and left on days 3, 4, and 5 at the same times of day.

The results are shown in Fig. 2. There seems to be a carry-over effect of atenolol for 24 hours, then

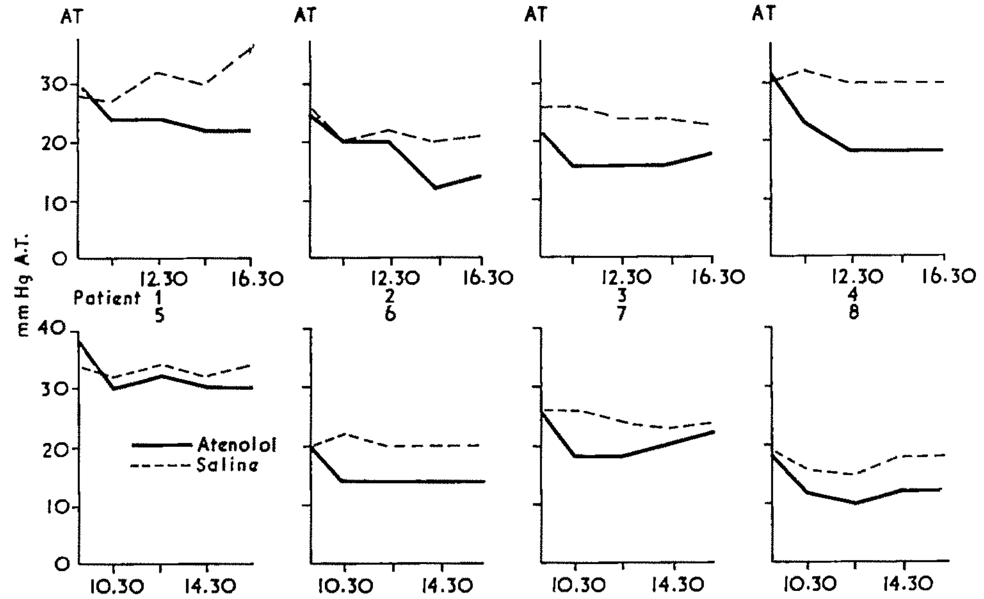

Fig. 1 *Applanation tonometry in the first tonometrised eyes (right eye for all except patient 5)*
(a) *after 1 dose of guttae atenolol 4% just after a reference tonometry at 0900 and* (b) *after 1 dose of guttae saline 0·9%*

Table 2 *Response to atenolol drops (after allowance for 'response' to saline drops on control day)*

Response to atenolol	*First tonometrised eye n=8 patients (mmHg)* *		*Second tonometrised eye n=7 patients (mmHg)*	
	Median	*Range*	*Median*	*Range*
Overall	5·6	3·2 to 13·2	3·5	0·8 to 10·8
At 1630 hours	6	1 to 16	2	−2 to 10

*The right cornea of 1 of the 8 patients was excluded from tonometry.
Overall response to atenolol = mean diurnal fall in pressure on atenolol − mean diurnal fall on saline (within patient).
Mean diurnal fall in ocular tension = tension at 0900 hours − mean tension at 1030, 1230, 1430, 1630 hours.

The fall in pressure was significant ($P < 0·05$) in both first tonometrised and second tonometrised eyes to a Wilcoxon Matched Pairs Rank Test.

some rise during the second day, and a further rise almost to the pretreatment level on the third day.

A second patient (No. 4) had guttae atenolol 4% for 2 months, was admitted on day 1, had tonometry on days 2, 3, 4, 5, and 8 at the same time as the other patient and was discharged on day 9. This time, in order to keep 1 eye as a control and to 'mask' the tonometrist more effectively, saline 0·9% was substituted for atenolol 4% in 1 eye only, the left. The change-over time, day 3, was unknown to patient and tonometrist (see Fig. 3). The pressure in the left eye (saline) gradually rises towards that in the right (atenolol), although the latter may also be tending to rise.

A much larger series would be required to be convincing, but there is an indication that the hypotensive effect after some weeks is less than in the first 12 hours. On the other hand, a longer period of tonometry after withdrawal of atenolol might have shown a greater rise of pressure, indicating a greater effectivity of this new drug after time than these patients show—unless a rebound effect occurred.

CONCENTRATION OF ATENOLOL

Our choice of 4% was rather arbitrary. A dose-response study would be useful.

COMBINATION WITH OTHER DRUGS

We consider that atenolol is likely to be given along with other drugs and not alone, if it will have a place at all in the treatment of glaucoma. We suggest, however, that even if the response to atenolol when combined with other drugs is less than its solitary effect it may well be therapeutically useful—it lacks the unpleasant side-effects of the miotics. Separate studies are required to assess whether its effect will be additive to (±adjuvant effect) or possibly subtractive from, say, pilocarpine, phospholine iodide, adrenaline, and acetazolamide.

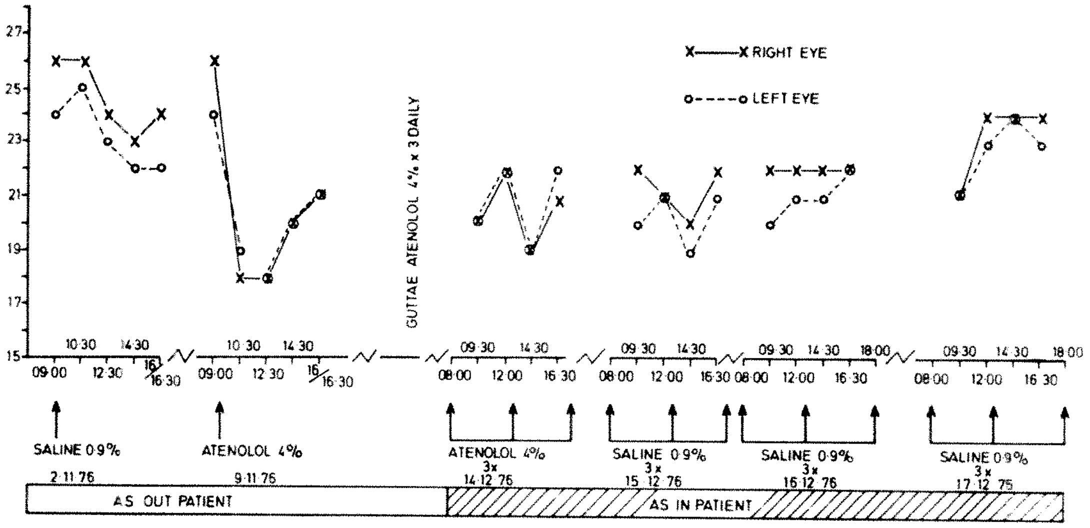

Fig. 2 *Patient 7. Note dramatic fall in pressure produced by guttae atenolol 4% right and left on 9 November 1976 as outpatient compared with saline 0·9% on 2 November 1976. The effect seems still maintained on 14 December 1976. Substitution of saline 0·9% in both eyes shows a definite rise of pressure of around 3 mmHg on the third day (? carry-over effect in the first day)*

Its effect in combination with guttae adrenaline will be particularly interesting since there may well be a positive interaction, i.e., a more than additive effect. Since it is known that α-stimulation (e.g., Pollack and Rossi, 1975) and β_2-*stimulation* (Patterson and Paterson, 1971) reduce ocular tension, and we now know that β_1-*blockade* reduces tension, the β_1-*stimulation* produced by adrenaline may well be reducing the latter's efficacy—so we suspect that pretreatment with atenolol may be necessary to

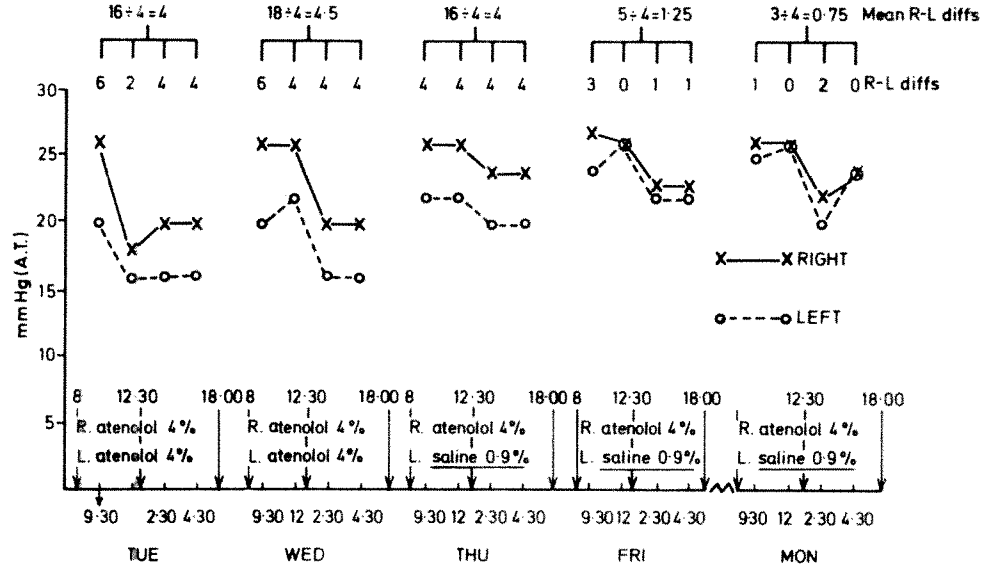

Fig. 3 *Patient 4, treated for the 2 previous months with atenolol 4% right and left. On the fifth day following substitution of saline 0·9% for atenolol 4% in the left eye only (the right continuing on atenolol 4%) the mean right and left difference becomes 0·75 mmHg compared with 4 and 4·5 on the first 2 days when atenolol 4% was given to both eyes*

achieve this adjuvant effect. Investigations have been started to elucidate this and also to compare the efficacy of guttae adrenaline and guttae atenolol. A more direct proof of β_1-stimulation's hypothesised ocular hypertensive activity would be to test the effect of guttae dobutamine, if that were practicable.

On the other hand, we suspect that pilocarpine may *reduce* atenolol's effect (unless the latter is given before the first dose of pilocarpine each morning). We guess that atenolol may cause its fall in pressure by reducing the amount of secretion of aqueous humour: presumably it may gain access to the ciliary epithelium mainly by diffusion through the ciliary muscle. That route would be blocked by the muscle spasm produced by pilocarpine; hence the expectation of interference with atenolol's effect. The necessary investigations are planned.

TOXICITY

Many patients will have to be treated for years before we can be confident that the many possible toxic side-effects do not arise, e.g., cataract, allergy, corneal changes. However, so far, in a series of about 6 patients treated for 3 to 4 months the drops have proved comfortable, non-irritant, and non-allergic.

We are grateful to ICI (Pharmaceuticals) Ltd for supplies of guttae atenolol 4% (Tenormin) and a research grant, and to Dr A. Rushton for much helpful discussion.

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Beta-adrenergic receptor blocking drugs: tear lysozyme and immunological screening for adverse reaction

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SUMMARY Patients who had received long-term therapy with practolol and other beta-adrenergic receptor blocking drugs were examined ophthalmologically. Tear lysozyme concentration and serum autoantibodies (antinuclear antibodies, DNA-binding antibodies and intercellular cement substance antibodies) were measured. It was found that beta-adrenergic receptor blocking drugs may have a pharmacological effect on the lachrymal glands, but this was not associated with dry eyes or adverse reaction. Practolol was found to be capable of reducing tear lysozyme concentrations to very low levels, and this was initially associated with high titres of ICC antibody. No other drug tested produced these effects.

Beta-blocking drugs are now used extensively in the treatment of patients with ischaemic heart disease, hypertension, and cardiac dysrhythmias, and they represent a great advance in the medical treatment of these conditions. However, they have produced side effects. The cardioselective beta-adrenergic receptor blocking drug practolol has been particularly notable in this respect (Editorial, 1975). Alleged side effects have also been reported on the skin and on the eyes with other beta-blocking drugs (Cumberbatch, 1974; Padfield *et al.*, 1975; Holt and Waddington, 1975; Knapp and Galloway, 1975; Clayden, 1975; Cubey and Taylor, 1975). However, the evidence has so far been open to doubt, and a number of alleged adverse ocular reactions have not been confirmed on further expert examination (Wright, 1975).

Ocular side effects of practolol have been described as an 'oculomucocutaneous syndrome' (OMCS), in which patients may suffer from reduced tear flow, conjunctival keratinisation, scarring, and shrinkage (Wright, 1975). A reduction of lysozyme and an absence of secretory IgA was found in the tear fluid of several patients. An absence of functional lachrymal gland tissue was reported in two cases of practolol OMCS which came to necropsy (Rahi *et al.*, 1976).

Indirect immunofluorescence has shown deposition of immunoglobulin in the intercellular spaces of xenogenic squamous epithelial tissue in 27 out of 29 cases of practolol-induced OMCS (Amos *et al.*, 1975). High titre antinuclear antibodies were also present in 22 out of 29 cases.

Tear flow can be difficult to estimate. Schirmer's test is misleading and inaccurate (Pinschmidt, 1970; Bijsterveld, 1973). Some reports of ocular side effects to beta-blockers have been based on this test. We believe that measurement of the tear lysozyme concentration is a better guide to lachrymal gland function, and we have developed a method for its quantitative estimation (Mackie and Seal, 1976). In a preliminary study this method was used to screen the lachrymal gland function of patients on practolol (Mackie and Seal, 1975).

We report now the results of our 2-year survey of patients on practolol, with and without an adverse reaction, together with patients on tolamolol, timolol, labetalol, and propranolol. We have examined all patients' eyes, have measured their tear lysozyme concentrations, and have estimated antinuclear antibodies (ANA) and intercellular cement substance (ICC) antibodies whenever possible.

Patients

Fifty-two patients on practolol were examined, 21 of whom had typical features of the OMCS in one or both eyes. Tear fluid and serum samples were collected at the same time. Thirty-five of these patients were followed up, and serial tear and serum samples were collected. Five patients on the cardioselective beta-blocker tolamolol were similarly studied and followed up. The duration of therapy

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for each of these two groups was at least 1 year. The male to female ratio was 0·8 : 1, and the mean age was 59.

Seventy-two patients on three non-selective beta-blockers were examined on one occasion only, and tear fluid and serum samples were collected. The male to female ratio was 1·5 : 1, and the mean age was 58.

Ten patients had taken timolol for 4 years and 13 had taken this drug for 1 year; 12 of these patients had taken low doses (5 to 20 mg/day), while 11 had taken high doses (25 to 40 mg/day). Sixteen patients had taken labetalol for 1 year and 10 had taken this drug for 6 months. Twenty-three patients had taken propranolol for at least 1 year. The tear lysozyme concentration was also measured in 70 healthy volunteers with no ocular disease and receiving no medication. The male to female ratio was 0·5 : 1, and the mean age was 50.

Methods

CLINICAL EXAMINATION

This was performed after the tear fluid samples had been collected with the filter paper discs. Patients were not allowed to use any eye drops for at least 2 hours before tear samples were collected, and in particular no antibiotic drops had been used on the day of the test.

External eye examination only was performed, and visual acuities were not measured. A general view of the eye was obtained under low-power microscopy. The depth of the marginal tear strips was observed. The lower lid was everted, and the conjunctiva of the lower fornix was assessed. The upper lid was raised slightly with the finger, and a small drop of fluorescein was instilled from a sterile minim (Smith & Nephew Ltd) so that it dropped from the conjunctiva above the superior limbus over the cornea. The tear film was then assessed for quality and break-up time. Any corneal staining or abnormality was noted. The Schirmer test was not used. The uptake of tears on the filter paper discs provided an indication of reflex tear flow. The upper lid was then everted, and the conjunctiva of the upper fornix was evaluated. It was considered that this examination was sufficient to allow the differential grouping of normal and abnormal eyes.

ESTIMATION OF THE TEAR LYSOZYME CONCENTRATION

Our original method (Mackie and Seal, 1976) was modified in order to process a larger number of specimens. Filter paper discs 5 mm in diameter were placed in plastic 30 × 10 mm tubes and were sterilised by gamma-irradiation. The disc and tube were weighed. The disc was then placed laterally in the lower conjunctival fornix until it was saturated with tears, when it was removed and replaced in the tube. The tube containing the disc was weighed again within 2 hours, the difference in weight being equivalent to the volume of tear fluid absorbed. Filter paper discs were similarly treated with 5 different standard solutions of calibrated egg-white lysozyme (Koch-Light Ltd). Two quality control solutions were also included.

All the discs were placed on a 25-cm square agar plate, previously flooded with *Micrococcus luteus* (*lysodeikticus*) and dried. The plate was incubated at 37°C for 18 hours. Zones of bacterial lysis were produced around the discs, and their diameters were measured in two directions with an image intensifier.

A linear regression line was produced from the logarithms of the different concentrations of the standard and the squared diameters of the lytic zones. This line was used to determine the concentrations of the controls and the patients' samples.

The tear lysozyme ratio was calculated for each sample. This was the ratio of the actual concentration measured to that of the lower limit of normality. This limit, which was established by our original method, varies with age. Calculation of this ratio thus allows direct comparison of all age groups.

ESTIMATION OF AUTOANTIBODIES

Antibodies to the intercellular cement substance of the baboon oesophagus were estimated by indirect immunofluorescence. All the sera were absorbed with human group A and B red blood cells before being titrated.

Antinuclear antibodies were estimated by indirect immunofluorescence using rat liver tissue. All these sera were diluted 1 in 10. Each sample was scored from negative to strong positive (++) according to the degree of fluorescent staining seen. Sera which gave a strong positive result were then titrated out. Anti-DNA antibodies were estimated by radioimmunoassay (Hughes, 1971).

The latex test was used to detect the rheumatoid factor.

Results

Results of tear lysozyme estimation are recorded as tear lysozyme ratios (right/left) on a logarithmic scale in Fig. 1. For patients from whom serial samples were collected the results shown are those measured nearest to the date on which therapy was stopped. For each group the statistical analysis is

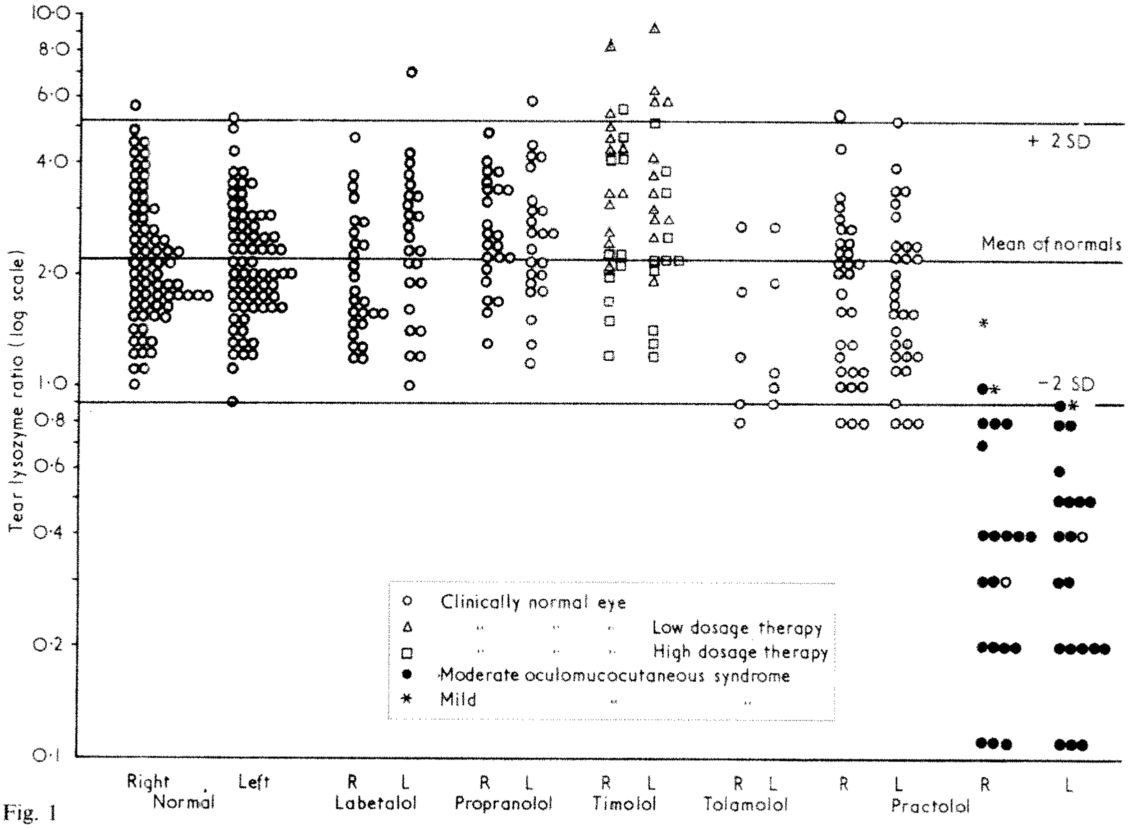

Fig. 1

Table 1 *Results of tear lysozyme ratios*

Beta-blocking drug	*No. of tear samples*	*Geometric mean tear lysozyme ratio*	*Significance*	
			Below normal	*Above normal*
Practolol				
OMCS	42	0·35	0·001	NS
clinically normal eyes	62	1·75	0·01	NS
Tolamolol	10	1·35	0·01	NS
Timolol				
low dose	24	3·83	NS	0·001
high dose	22	2·41	NS	NS
Labetalol	50	2·18	NS	NS
Propranolol	46	2·46	NS	0·05

NS: Not significant

given in Table 1 and autoantibody results in Table 2.

The tear lysozyme ratios of the healthy volunteers followed a normal (Gaussian) distribution. The 95% confidence limits for the geometric mean value of this normal population were 2·01 to 2·33.

PATIENTS WITH ADVERSE OCULAR REACTION DUE TO PRACTOLOL

Patients complained of dry, gritty eyes that burned and were sore. On examination there was evidence of dryness, corneal erosions, and/or conjunctival

Table 2 *Results of autoantibody screening*

Beta-blocking drug	*No. of serum samples*	*Intercellular cement antibody*			*Antinuclear antibody*	
		1/20	*1/40*	*≥1/80*	+	++
Practolol						
OMCS	20	0	0	16	—	—
clinically normal eyes	19	2	0	1	5	2* (1/80 and 1/160)
Tolamolol	5	2	0	1	1	0
Timolol	22	2	0	0	1	0
Labetalol	16	0	0	0	1	1* (1/160)
Propranolol	17	1	1	0	2	0

*Anti-DNA antibody within normal limits

scarring. Mild and moderate cases were encountered, several with dubious scarring on initial examination, that progressed in severity over a few months.

Seven patients who had stopped practolol within the preceding 2 months were affected in both eyes. They had low right and left tear lysozyme ratios ($<$0·1 to 0·8/$<$0·1 to 0·9) and 6 out of 7 had high titre ICC antibody. One year later, with no evident clinical recovery, their tear lysozyme ratios were still low ($<$0·2 to 0·8/$<$0·2 to 0·8); 4 out of 6 had lost their ICC antibody.

Eleven patients who were affected in both eyes were examined on one occasion only, after they had stopped practolol. Their tear lysozyme ratios were low in both eyes ($<$0·1 to 1·0/0·1 to 0·75), and 7 out of 10 had high titre ICC antibody.

Two patients with normal or marginally affected right eyes had well-marked symptoms and signs in the left eyes, with low left tear lysozyme ratios (1·6/0·5 and 1·5/0·6), and both had high titre ICC antibody. One year later, with no evident clinical recovery, their left tear lysozyme ratios were still low (1·9/0·3 and 1·3/0·5); both had lost their ICC antibody.

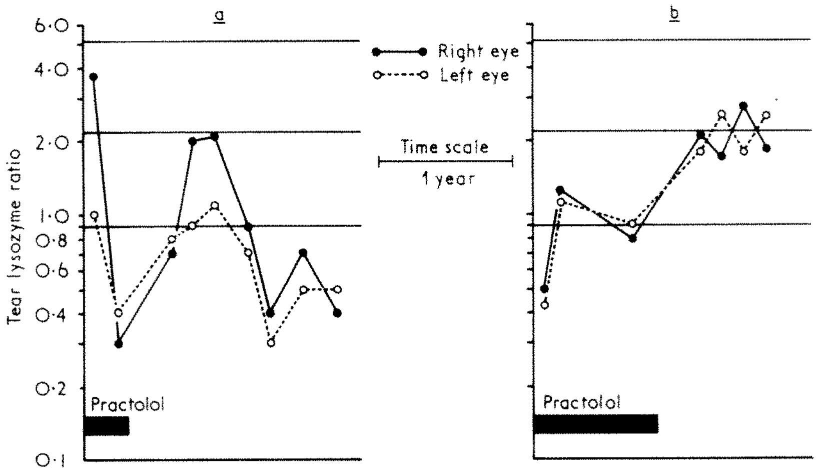

Fig. 2

One patient, previously described as case 17 (Mackie and Seal, 1975), had a striking fall in the tear lysozyme concentration before developing an adverse ocular reaction. After practolol was stopped the tear lysozyme ratio increased in the right eye to normal levels but has since fallen, with that of the left, to consistently low levels (Fig. 2*a*). The patient had initially a high titre of ICC antibody, but nine months after stopping practolol it was no longer present. The patient's clinical condition remains unchanged.

One patient stopped practolol of his own accord when he developed dry, burning eyes; he kept his eyes moist with instilled fluids for 2 months, after which he recovered from his symptoms. Clinical examination showed no signs of adverse ocular reaction, but his tear lysozyme ratios were low (0·4/0·6); at that time sclerosing peritonitis also appeared. Nine months later his tear lysozyme ratios were normal (1·6/1·4) and he had no ICC antibody.

PATIENTS WITH NORMAL EYES ON CLINICAL EXAMINATION

Patients on practolol

One patient had fluctuating, low tear lysozyme ratios in both eyes, which increased to normal levels when practolol was stopped (Fig. 2*b*). Reflex tear flow during this period was normal and no autoantibodies were present. Two patients each had a low tear lysozyme ratio in one eye only (1·2/0·8 and 0·8/1·4). The ratios increased to normal levels (2·1/2·1 and 2·7/3·1) after practolol was stopped, and no autoantibodies were then found. Two patients had low right and left tear lysozyme ratios (1·0/0·8 and 0·8/0·8) while on practolol, but refused to be followed up.

One patient presented with a high titre of ANA but had no anti-DNA or ICC antibodies. Six months later, and 3 months after stopping practolol, the patient developed a high titre of ICC antibody; her eyes and tear lysozyme ratios were normal. Six months later sclerosing peritonitis was diagnosed at laparotomy. This indicates that practolol-induced systemic lupus erythematosus (SLE) probably preceded the practolol toxicity as evidenced by the sclerosing peritonitis.

Patients on tolamolol
Two patients had low tear lysozyme ratios (0·9/0·9 and 0·8/1·0). Since stopping the drug one has regained normal levels (1·1/1·7) in the left eye, while the other patient has fluctuated in the marginal range. Neither patient developed autoantibodies.

One patient was observed to develop high titre ICC antibody but appeared clinically normal. The titre increased from 1:20 to 1:80 over a period of 4 months.

Patients on timolol, labetalol, and propranolol
The patients had normal tear lysozyme ratios except those on low doses of timolol, who had significantly increased levels. One patient on labetalol had a high titre of ANA, with a normal titre of anti-ANA antibody; this suggests that the ANA could be drug-induced.

Discussion

Patients with keratoconjunctivitis sicca have dry, irritating eyes with poor tear flow, together with reduced levels of tear lysozyme (Erickson, 1955; McEwen and Kimura, 1955). Patients with practolol-induced OMCS have similar symptoms, and estimation of the concentration of their tear lysozyme has given very low values; no clinical improvement has occurred after 1 year and the tear lysozyme concentrations have remained very low.

Patients with clinically normal eyes on various doses of practolol or tolamolol had significantly reduced concentrations of tear lysozyme; several low values were found which increased to normal after therapy was stopped. Patients with clinically normal eyes on low doses of timolol had significantly increased concentrations of tear lysozyme, while those on high doses were within normal limits. There is evidence to suggest that low doses of timolol given intraveneously may produce a mild sympathomimetic effect, which is not, however, observed at high dosage (Richardson, P. J., 1976, personal communication).

The lachrymal gland is supplied by parasympathetic and sympathetic nerves, but the function of the sympathetic supply is obscure (Duke-Elder, 1968; Adler, 1970). Intravenous adrenaline has been shown experimentally in cats to stimulate tear production, but its content was not analysed (Maes, 1938). We suggest that practolol and tolamolol, β_1-selective blocking drugs, may depress the secretion of tear lysozyme, while low doses of timolol may stimulate it.

Practolol-induced SLE and adverse ocular reaction are associated with high titres of ANA, as are some cases of adverse cutaneous reaction (Raftery and Denman, 1973; Felix *et al.*, 1974; Amos *et al.*, 1975). Apparently unaffected patients on practolol therapy may also develop high titres (Raftery, 1974). High titres of ANA have preceded some cases of procainamide-induced SLE (Fakhro *et al.*, 1967). It is interesting that the metabolite N-acetylprocainamide bears a structural resemblance to practolol (Davies *et al.*, 1975). Our findings show that 2 out of 19 patients on practolol and 1 out of 16 on labetalol, with no clinical adverse reactions, had high titres of ANA with normal levels of anti-DNA antibody. However, one of the patients on practolol, with a high titre of ANA and later ICC antibody, developed sclerosing peritonitis over the following year.

Pemphigus (natural and drug-induced), burns, practolol toxicity, and long-term therapy are associated with high titres of ICC antibody (Anderson *et al.*, 1970; Thivolet *et al.*, 1970; Amos *et al.*, 1975; Behan *et al.*, 1976; Davies and Holt, 1976; Gange *et al.*, 1976). We have found such high titres in 16 out of 20 patients with practolol-induced OMCS, as well as in 1 out of 19 and in 1 out of 5 patients on long-term therapy with practolol and tolamolol respectively.

The incidences of low titres of ANA and ICC antibody in all groups were within normal limits. No patients had the rheumatoid factor.

Estimation of tear secretion (by Schirmer's test) and estimation of ANA before and during therapy with some beta-blockers have been suggested as screening tests for adverse drug reaction (Felix *et al.*, 1974; Richardson *et al.*, 1975). We suggest that any patient who complains of a dry eye while on therapy with a beta-blocker, particularly a β_1-selective blocker, should be examined by an ophthalmologist and the tear lysozyme ratio be estimated on three occasions. If this ratio oscillates to less than 0·9, it is significantly reduced and is suggestive of impaired lachrymal gland function. Although expert ophthalmological examination will usually show if any abnormality exists, it is not always available; furthermore, the tear lysozyme ratio may be low before clinical signs of adverse ocular reaction appear. Although the mechanism of adverse reaction to beta-blockers is obscure, it seems advisable to test all patients on beta-blockers for ANA and ICC antibody, since high titres may occur before clinical signs of an adverse drug reaction appear.

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Astigmatism in cataract surgery

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SUMMARY We report on our investigation into astigmatism in 40 eyes following a corneal cataract incision closed with a continuous 10/0 nylon monofilament suture (Ethilon). Immediately after surgery there was astigmatism caused by the nylon suture (suture-induced astigmatism), its severity depending on the tightness of the suture. It ranged from 1 to 10·5 dioptres, the mean value 4·09 dioptres with a standard deviation of ±2·5. Removing the nylon suture eliminated this astigmatism and within a few weeks the corneal astigmatism correction in 48% of eyes returned to the preoperative level. In 80% of eyes the difference between the final postoperative corneal astigmatism (4 months after removing the continuous suture) and the preoperative astigmatism was 0·75 dioptres or less and the maximum change was 1·5 dioptres. In 40% of eyes the axis of the cylinder changed from a horizontal to an oblique axis but did not change from a with- to against-the-rule axis.

The degree of astigmatism remained constant while the suture was in place and in 50% of eyes was equal to or less than 3 dioptres. The mean of the spherical equivalents was 11·31 dioptres with a standard deviation of ±1·25. A spectacle correction 14 days after operation prescribed either as the mean spherical equivalent (11·50 dioptres) or according to the patient's refraction will give satisfactory vision until the suture is removed 4 months after operation.

The degree of astigmatism following a corneal section and continuous nylon suture compares very favourably with astigmatism following other suturing techniques for cataract.

Improvements in the surgical technique of cataract extraction and the desire to minimise complications have focused attention on the cataract incision and its closure. As a result suture materials have been developed which can be more accurately placed within the incision, allow excellent anatomical apposition, and cause less postoperative irritation and reaction.

The most suitable suture materials at present available for cataract surgery are virgin silk and monofilament nylon. The monofilament nylon (10/0) is less irritating, the eye postoperatively is quieter, and the irregular incisional scars associated with ulceration and extrusion of virgin silk are eliminated. It has the added advantages that the material is elastic and is not extruded, so that it can be used as a continuous suture. Tissue reaction to the nylon is minimised and scar formation is delayed, so that the nylon is left in the incision for 3 to 4 months. The prolonged, firm, and anatomically precise apposition of the incision produces a neater scar.

A survey of the literature indicated that there is little knowledge of the amount of astigmatism caused by continuous nylon sutures (Lamcke *et al.*, 1971; Boke *et al.*, 1971; Troutman, 1973). We have designed a study to measure this and the factors that influence it. A previous study (Luntz and Livingston, 1976) showed that the type of suture material and/or suturing technique does not significantly influence the final postoperative astigmatism. This study and other studies of post-cataract astigmatism do not include a corneal section with a continuous nylon suture and do not measure 'suture-induced' astigmatism.

We have investigated the effect of a continuous nylon suture in a corneal section on the final postoperative astigmatism (after removal of sutures and normalisation of suture-induced astigmatism) and whether this is influenced by the level of suture-induced astigmatism.

Subjects and methods

We report a prospective study in 40 eyes of 32 patients. This number comprises all cataract patients operated on by one of us during 1975 (M.H.L.) in whom a corneal section was closed by a continuous 10/0 monofilament nylon suture (Ethilon) in a running shoe-string configuration as

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used by Ryan and Maumenee (1973) but in a limbal incision under a conjunctival flap. Keratometer (K) readings were taken preoperatively and at 6 weeks after operation. The sutures were removed after 4 months, the 'K' readings taken, and repeated 4 months later. The last reading was taken for the purpose of this study as the final postoperative corneal astigmatism. Refraction was done 6 weeks after operation and 4 months and 8 months later. To follow the course of postoperative corneal astigmatism in greater detail the 'K' readings in 5 eyes were taken preoperatively and 2 weeks and 4 months postoperatively when sutures were removed. These were repeated at 4 weeks, 6 weeks, and 4 months after removal of the sutures.

A standardised surgical technique was used. The eye was opened by cutting a groove extending for 150° (from the 9 o'clock to 2 o'clock position) over the upper half of the cornea immediately anterior to the corneo-scleral limbus and to two-thirds of the corneal depth. The anterior chamber was perforated at the right-hand corner of the groove and the section completed with corneal scissors cutting to the left, the scissors held vertically. The result was a 2-plane incision with a corneal bevel in the deep one-third. The incision was closed with a continuous 10/0 nylon suture which resembled a closed boot-lace (Fig. 1). The first suture was placed at the right-sided end of the incision to the level of Descemet's membrane and radial to the incision, followed by 4 deep, radial bites across the incision, the thread remaining continuous. Loops were moved to either side of the incision to keep them out of the way, and the lens was extracted.

After extraction of the lens the continuous suture was completed with 4 sutures placed from left to right across the length of the incision, each one at midpoint between the deep sutures, at a level of half the corneal depth and parallel to the succeeding deep suture. The 2 free ends were tied and the knot was buried in the cornea on the scleral side. The use of deep and superficial bites ensures good apposition of the endothelial and epithelial surfaces. It is important only to approximate the incision edges without drawing the suture up too tightly. The anterior chamber was filled with balanced salt solution to ensure a watertight closure.

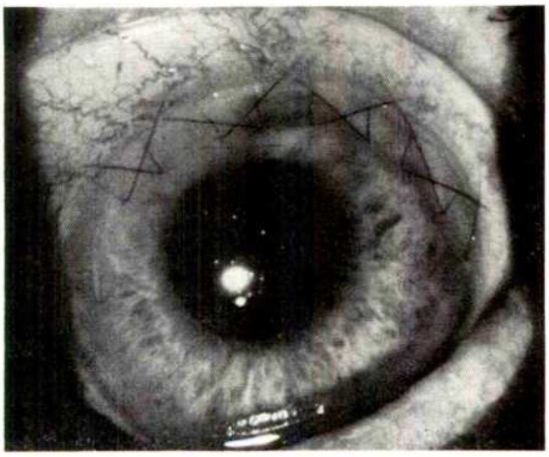

Fig. 1 *Photograph of 'boot-lace' type of continuous 10/0 nylon (Ethilon) suture used to close a corneal cataract section.* ×10

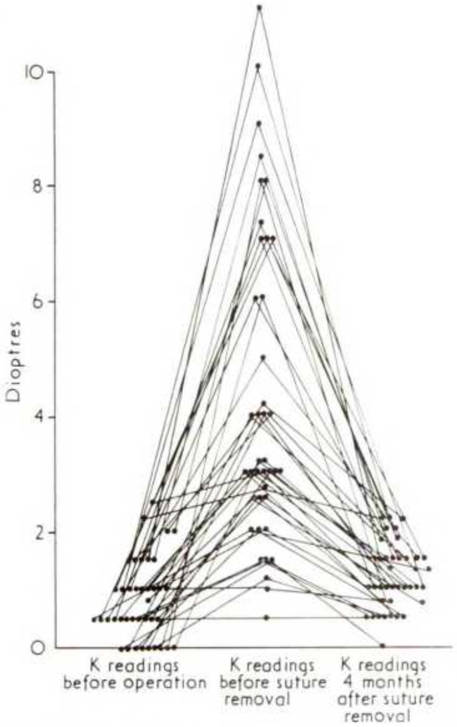

Fig. 2 *Corneal astigmatism ('K' readings) before and after a corneal cataract incision closed by a 'boot-lace' type of continuous 10/0 nylon (Ethilon) suture in 40 eyes. Postoperative astigmatism is recorded after 6 weeks with the suture in place and 4 months after removing the suture. The 3 measurements for each eye are separately plotted and each joined by a continuous line. The astigmatism is significantly increased 6 weeks after surgery owing to the suture. The final postoperative astigmatism (4 months after removing the suture) approximates the preoperative values*

Results

CORNEAL ASTIGMATISM

Preoperative corneal astigmatism and the astigmatism at 6 weeks and 8 months after operation in

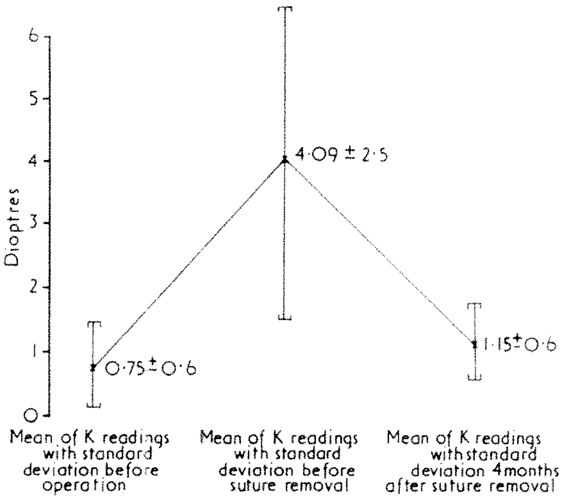

Fig. 3 *Corneal astigmatism ('K' readings) in 40 eyes with cataract incisions closed with a 'boot-lace' type of continuous 10/0 nylon (Ethilon) suture. The mean values and the standard deviations of the preoperative 'K' readings (the first plot), the astigmatism caused by the suture measured 6 weeks after operation (the second plot), and measured 4 months after removal of the sutures (third plot)*

40 eyes are recorded graphically in Figs. 2 and 3. The values for each eye are individually plotted in Fig. 2, while Fig. 3 records the mean values and their standard deviations. The graphs demonstrate dramatically how corneal astigmatism was increased when measured 6 weeks after operation with the nylon sutures in place. Half the eyes had corneal astigmatism of between 0 and 3 dioptres. The higher readings, which ranged from 3 dioptres to 10·5 dioptres of cylinder, occurred early in the series and resulted from closing the suture too tightly, causing excessive distortion of the corneae. We subsequently corrected this fault and reduced the level of astigmatism. The mean astigmatism before operation was 0·75 dioptres, SD ±0·6, with the suture in place 4·09 dioptres, SD ±2·5, and 4 months after removing the suture 1·15 dioptres, SD ±0·6.

The second point that these graphs demonstrate is the dramatic drop in the magnitude of corneal astigmatism once the sutures were removed. In most eyes the final postoperative corneal astigmatism was about the same as the preoperative measurement and in 2 eyes less. It did not exceed 2·25 dioptres and was independent of the magnitude of the astigmatism caused by the suture (Fig. 2).

ASTIGMATISM BY REFRACTION

Objective refraction to give an accurate estimate of astigmatism before operation was not possible in all our cases because lens opacities interfered with or obstructed the reflect. However, objective refractions were done 2 weeks after operation (with the continuous suture tied in the cornea) and at 2 and 4 months after removal of the continuous suture. The results are plotted in Fig. 4 and are expressed as minus cylinders. The first plot 2 weeks after operation represents the astigmatism measured by refraction and caused by the suture, in 55% of eyes between 1·5 and 3 dioptres. Once the sutures were removed astigmatism dropped within 4 weeks to the final postoperative level and remained constant.

SUTURE-INDUCED AND SURGICALLY INDUCED ASTIGMATISM

The above measurements reflect astigmatism measured with the suture in place and after its removal.

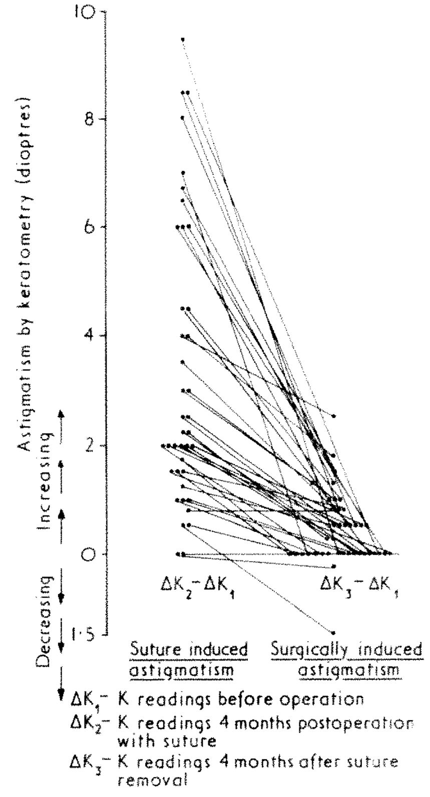

Fig. 4 *Astigmatism by refraction in 40 eyes with a cataract section closed by a 'boot-lace' type of 10/0 nylon (Ethilon) suture measured at 2 weeks after operation (first plot) and at 2 months (second plot) and 4 months (third plot) after removal of the sutures. Measurements are expressed as minus cylinders. The graph demonstrates the astigmatism caused by the suture (first plot) and the rapid return to preoperative levels after removal of the suture (second and third plots)*

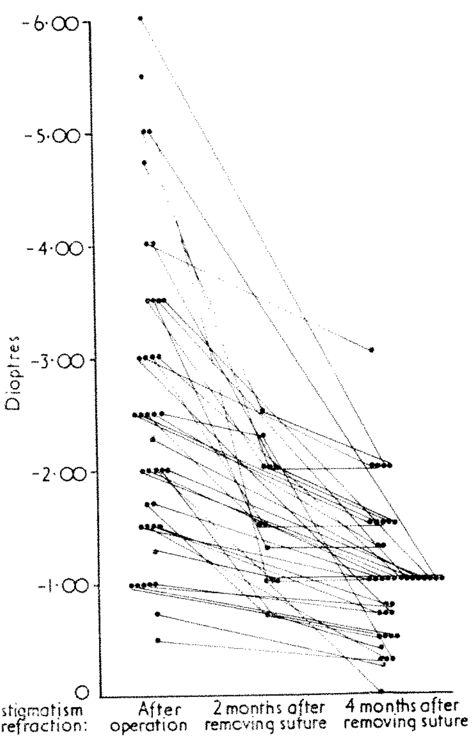

Fig. 5 *The suture-induced corneal astigmatism ('K' readings before operation subtracted from the 'K' readings with the sutures in place read 6 weeks after operation) is plotted closest to the abscissa. It measures up to 2·0 dioptres in 97% of eyes. The surgically induced astigmatism ('K' readings before operation subtracted from the final 'K' measurement 4 months after removing the suture) is plotted farthest from the abscissa. There is no surgically induced astigmatism in about half the eyes and it does not exceed 1·5 dioptres*

They do not, however, reflect the actual amount of astigmatism (or corneal distortion) produced by the suture (suture-induced astigmatism) and by the scarring process of the operation (surgically induced astigmatism). The suture-induced astigmatism is obtained by subtracting the astigmatism measured with the suture in place from the preoperative measurement and the surgically induced astigmatism by subtracting the astigmatism after removal of the sutures from the preoperative reading. These results in terms of corneal astigmatism are recorded graphically in Fig. 5. Suture-induced astigmatism is plotted closest to the abscissa, surgically induced astigmatism farthest from it. The former was less than 2 dioptres in 97% of eyes; only 1 eye exceeded 2 dioptres. There was no surgically induced astigmatism in about half the eyes (these plots lie on the base of the ordinate). This point is further emphasised in Fig. 6, which records the pre- and postoperative corneal astigmatism. In 48% of eyes there was no change from the pre- to postoperative level; in 2 eyes the astigmatism after operation was actually less than before operation. These two results are plotted below the abscissa in Fig. 5.

In 5 eyes the behaviour of the pre-suture-removal and post-suture-removal corneal astigmatism was followed in more detail, and these results are plotted in Fig. 7. The level of suture-induced astigmatism is reached at 2 weeks after surgery and remains constant after this. After removal of the sutures the astigmatism drops rapidly to reach the final postoperation level within 4 weeks and remains relatively constant at this level.

CHANGES IN CYLINDER AXIS

In 60% of eyes the cylinder axis measured after removal of the suture and compared to the preoperative finding remained unchanged (Table 1). If the cylinder axis did change it changed from a horizontal to an oblique direction, but not from with to against the rule.

SPHERICAL EQUIVALENTS

The spherical equivalent calculated from the 'K' readings with the sutures in place was 11·31 dioptres (mean value) with a standard deviation of ±1·25.

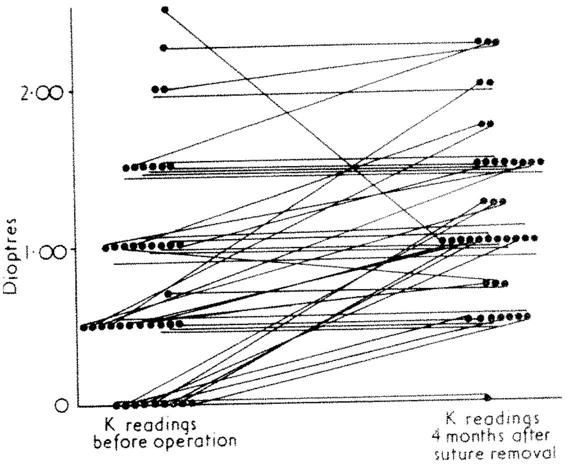

Fig. 6 *The 'K' readings before and after cataract surgery in 40 eyes. Corneal astigmatism before the operation is plotted closest to the abscissa and corneal astigmatism 4 months after the removal of the continuous 10/0 nylon suture is plotted farthest from the abscissa. In the majority of eyes the change from preoperative to postoperative astigmatism is minimal. In 2 eyes the postoperative astigmatism was less than the preoperative and the sum of the two becomes a plus instead of minus. These plots are recorded below the ordinate*

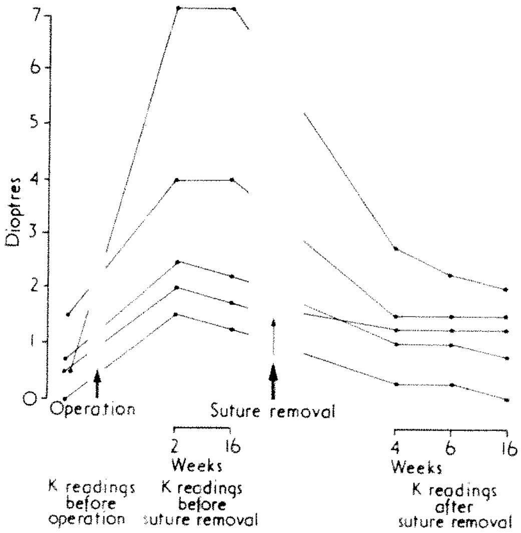

Fig. 7 *A corneal cataract section was made in 5 eyes and closed with a continuous 'boot-lace' type of 10/0 nylon (Ethilon) suture. Corneal astigmatism was measured at 2 weeks and 16 weeks after the operation, with the suture in the cornea, and at 4 weeks, 10 weeks, and 16 weeks after removal of the suture. The graph demonstrates the relative stability of the astigmatism caused by the suture from 2 weeks after the operation*

The mean postoperative spherical equivalent (4 months after removal of the suture) calculated from the 'K' readings was 11·85 dioptres with a standard deviation of ±1·8 (Table 2).

Discussion

Lack of knowledge about the degree and properties of suture-induced astigmatism has deterred many surgeons from using nylon sutures in cataract surgery and in particular a continuous nylon suture, a technique that has a number of obvious advantages. Tension of the suture is equally distributed throughout the depth of the incision, ensuring good anatomical apposition. Individual sutures can be more accurately placed in relation to each other. Surgical knots are kept to a minimum, thus eliminating another source of postoperative irritation and reaction.

Table 1 *Change in direction of cylinder axis from preoperative 'K' measurement to post-suture removal 'K' measurement*

Change of axis	*Number of eyes*	*Percentage*
No change	24	60
Zero to oblique (<45°)	3	7·5
Zero to with the rule (<45°)	1	2·5
Zero to against the rule (<45°)	4	10
≃ 45°	8	20
With to against the rule (90°)	0	0
Total	40	100

Table 2 *Mean of postoperative spherical equivalents*

Suture	*Number*	*Mean*	*SD*
Nylon 10/0 interrupted	32	10·7	2·8
Virgin silk 8/0 interrupted	17	11·7	1·9
Nylon 10/0 continuous under conjunctival flap	22	10·6	0·58
Nylon 10/0 continuous in corneal section	40	11·85	±1·8

No statistical significance (t test)

As the nylon incites little tissue reaction and remains fixed in its suture bed, corneal distortion (astigmatism) produced when the suture is tied should remain constant while the suture is in place. It should disappear when the suture is removed.

Suture-induced astigmatism is not a problem with virgin silk or absorbable sutures which are placed as edge-to-edge, interrupted sutures. Postoperative tissue oedema and even necrosis within individual sutures cause them to cut out and release tension on the incision, and virgin silk is extruded. Consequently the cornea tends to regain its original shape, minimising astigmatism. To eliminate suture-induced astigmatism from nylon sutures requires their removal, which is easier if the incision is corneal rather than subconjunctival. Hence the preference for a corneal section.

Every eye in this study developed some degree of suture-induced astigmatism. In half of them it did not exceed 3 dioptres (Fig. 2).

Once established (14 days after operation) the degree of astigmatism remained constant until the suture was removed (Fig. 7), its magnitude being in direct proportion to the tightness of the suture. The suture should be tightened only enough to approximate the wound edges. The fact that suture-induced astigmatism remained constant meant that patients could be fitted with a cataract spectacle 2 weeks after surgery that tided them over the 3 to 4 months postoperatively until the continuous suture was removed. The cataract correction was dispensed either according to the patient's refraction or as a +11·50 dioptre sphere, which was the mean of the suture-induced spherical equivalents.

Once the suture was removed the astigmatism dropped significantly within 4 weeks, and the final

Table 3 *Difference of pre- and postoperative astigmatism (keratometry)*

Suture	*Number*	*Mean*	*SD*
Nylon 10/0 interrupted	31	−1·6	1·2
Virgin silk 8/0 interrupted	18	−0·6	1·6
Nylon 10/0 continuous under conjunctival flap	11	−0·9	2·0
Nylon 10/0 continuous in corneal section	40	−1·15	0·6

No statistical significance (*t* test)

postoperative astigmatism was not significantly changed from the preoperative value, nor was it influenced by the magnitude of the astigmatism caused by the suture (Figs. 2 and 3). In 48% of eyes the pre- and postoperative corneal astimatism were the same, and in 80% the change was equal to or less than 0·75 dioptres (Figs. 5 and 6), testimony to the fact that a continuous 10/0 nylon suture achieves and maintains excellent apposition of the incision.

In 40% of eyes the axis was displaced obliquely, probably the result of a tendency to tilt the incision to the right side (the incision was made from the 9 o'clock position to the 2 o'clock position), allowing better use of the exposure for a right-handed surgeon when removing the lens. In none of them did it change from with to against the rule (Table 1).

The preponderance in this study of with-the-rule astigmatism following cataract surgery and of oblique astigmatism, the flat meridian moved vertically, which can be explained by an obliquely placed incision, confirms the findings of an earlier investigation (Bedrossian *et al.*, 1969).

In a previous publication we compared the final postoperative corneal astigmatism and spherical equivalent in scleral cataract incisions closed by interrupted 8/0 virgin silk, interrupted 10/0 nylon (Ethilon), and a continuous 10/0 nylon (Ethilon) under a conjunctival flap (Luntz and Livingston, 1976). Adding these to our presently reported results and comparing them (Tables 2 and 3) one finds that there is no statistically significant difference.

The conclusion is that astigmatism resulting from cataract surgery is not influenced by the suturing technique within the framework of those used in our studies or by the choice of material (monofilament, nylon, or virgin silk). It may be influenced by the type of incision (Bedrossian *et al.*, 1969). A standard incision was used in all these studies, although the site of the incision changed from the scleral side of the limbus to the corneal side of the limbus. This factor is at present being investigated.

This work was supported by a grant from the University of the Witwatersrand Senate Research Council.

Results reproduced in Tables 2 and 3 from 'Surgery of Astigmatism', pp. 226–230 in *Advances in Ophthalmology*, Vol. 33 (Kager, Basel) and reproduced with permission of the editors.

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Book reviews

Progress of Lens Biochemistry Research: Ophthalmologica Proceedings Series. Vol. 8. Edited by A. HOCKWIN. 1976. Pp. 316, 124 figs., 67 tables, refs. Junk, The Hague (Dtch. Glds. 95)

This is a review volume comprising papers by some 33 authors in honour of Professor Dr Med. J. Nordmann. The first few papers give an interesting account of morphological changes as revealed by the electron microscope in galactose and diabetic cataract. Others deal with tissue culture of the lens epithelium.

In one paper it is shown that lens fibres can again become undifferentiated, and the cells so formed appear identical to those composing the original lens epithelium. Other topics dealt with in detail include factors affecting mitosis, the relationship of proteolytic enzymes and calcium content to cataract formation, the biochemistry of ageing changes, and cataracts induced by toxic agents.

This book should be read by all those actively engaged in the biochemical and metabolic aspects of crystalline lens research.

R. F. FISHER

XIIth ISCERG Symposium, Clermont Ferrand, 20–22 May 1974. Edited by R. ALFIERI and P. SOLÉ. 1976. Junk, The Hague (Dtch. Glds. 125)

The twelfth ISCERG symposium was held in 1974 and unfortunately there has been some delay in the publication of the papers. However, the volume provides a useful insight into recent developments in electrodiagnostic ophthalmology. There are several useful papers on electroretinography and electrooculography in relation to macular function, and the meeting opened with two good reviews of relevant advances in the anatomy of the retina and visual pathways. Several of the free papers are of interest, ranging from the measurement of saccadic eye movements by electrooculography to an analysis of the waveform of the electroretinogram in Oguchi's disease. The four papers on the visually evoked response reflect the increasing interest in this aspect of visual function, and give hope for future clinical applications.

N. GALLOWAY

Symposium on Ocular Therapy. Vol. 9. Edited by I. H. LEOPOLD and R. P. BURNS. 1976. Pp. 161, figs., tables, refs. John Wiley, Chichester ($13·75)

This latest volume in a popular series has yet again managed to introduce new material with 21 authors writing 12 chapters on a wide variety of subjects. There are two interesting chapters on methods of prolonging local drug action. Maichuk describes work in the USSR on four polymeric drug delivery systems including an erodable insert (SODI), and Pavan Langston reviews experience with non-erodable inserts (Oculoserts), both authors quoting trials in glaucoma, herpes keratitis, and trachoma. Kaufman describes progress in antiviral agents, Leopold considers the site of action of anti-inflammatory agents—a useful chapter for those wishing to be brought up to date in the changing field of immuno regulation.

In a study of endophthalmitis vitreous aspiration was found to be of more value than anterior chamber paracentesis and the safety of intravitreal injection of gentamicin is examined. Some theoretical considerations of injection of drugs into the vitreous are described by Maurice. There is an excellent description of practolol toxicity from Wright and Fraunfelder, also a review of platelet inhibition therapy in occlusive vascular disease, and an interesting article on compliance in patient therapy from Kass and Becker. Other subjects include the experimental uptake of epinephrine in aphakic animals, haloperidol mydriasis, and cycloplegia. The book finishes with a useful review of tissue adhesives.

Though the cost may deter some purchasers the volume is well produced with good illustrations.

S. J. CREWS

Epidemiology of Onchocerciasis. Report of a WHO Expert Committee. Technical Reprint Series 597, 1976. Pp. 94, figs., refs. World Health Organisation, Geneva (Swfr7)

This third report of a WHO Expert Committee on Onchocerciasis states quite rightly that the last 10 years have seen considerable advances in knowledge of this disease and of its epidemiology. These are reported under the following headings: the disease, the parasite, the vectors, *Onchocerca—Simulium* complexes, human host factors, environmental and socioeconomic factors, and diagnosis (including immuno-diagnosis); finally, there is a detailed description of the special epidemiological features of onchocerciasis and the evaluation of control programmes. The Volta River Basin Area Control Programme is described in some detail.

A main feature of the booklet is that it points out the gaps in knowledge of the disease, and each chapter ends with short paragraphs on research needs. Since the WHO gives priority to onchocerciasis under the new special programme of research and training in tropical diseases, there is a good chance that funds will be made available for research projects following the recommendations outlined here.

Relatively little priority has been given to ocular onchocerciasis considering it is this aspect which justifies costly control programmes. Only 1 of the 14 main contributors is an ophthalmologist. The ocular field is wide open, and it is hoped that this booklet will encourage more ophthalmologists to become actively involved in this fascinating parasitic panophthalmitis.

JOHN ANDERSON

Contact Lenses and Corneal Disease: A Programmed Course. A. R. Gasset. 1976. Pp. 401, figs., tables. Appleton-Century Crofts, New York (£17·55)

This paperback manual is in the style of a programmed course with each page divided into two columns, that on the left containing a series of simple statements, totalling 1245 in the book as a whole. Beneath each of the statements is a question relating to it and the answer is in the right-hand column opposite.

Many of the questions are of such an obvious nature, however, that they merely tend to irritate rather than inform the reader. This criticism apart, the sections on the use of the keratometer and fitting both hard and soft contact lenses form a clear, basic introduction to the practical aspects of the subject. The second half of the book is concerned with the therapeutic uses of contact lenses and corneal disease but, unlike contact lens fitting, the subject of this section does not in general lend itself to such a method of presentation. In addition, it suffers from a lack of adequate illustrations, those which are provided being of poor quality which contribute little to the text. The methods of treatment which are advised seem both accurate and up to date, although the wisdom of advocating the unqualified use of constant-wear soft lenses in severe dry eye states must be seriously questioned.

This book can be recommended to ophthalmologists who require an introduction to the basic aspects of contact lens fitting, but if they wish to take up the specialty seriously it would be essential to complement this initial outline of the subject with more extensive reading from established texts. P. D. DAVIES

Surgery of the Eyelids and Lacrimal System. L. T. Jones and J. L. Wobig. 1976. Pp. 241, 222 figs., 4 tables, bibliog. Alabama, Aesculapeus Publ. Co., Birmingham, Alabama ($45)

Intended for ophthalmic plastic surgeons, this book summarises the views expressed over the years by Dr Lester T. Jones and his associates on the causes and management of disorders of the lids and lacrimal apparatus. The section on anatomy and physiology makes compulsive reading coming from such an established authority on the subject. The text is liberally illustrated, mostly with black-and-white photographs which vary considerably in quality.

Most British ophthalmologists will, I think, be surprised to see such prominence given to aponeurotic repair for the management of ptosis, particularly when levator resesection is barely mentioned. The message of caution to the advocates of the tarsomullerectomy operation is timely. In discussing the preoperative assessment of patients with epiphora the authors rely almost entirely on the use of dye tests, with only passing mention of dacryocystography and no reference to the more sophisticated investigations such as intubation and subtractive macrodacryocystography or scintillography which are now available.

In their preface the authors state that the book is not a complete work on the subject and presents only concepts with which they have had personal interest and experience. While not agreeing with all the methods advocated, I am sure that all surgeons who operate in this specialised field will find much to provoke thought and, in addition, a great deal of useful and practical information. R. A. N. WELHAM

International Symposium on Fluorescein Angiography, Ghent, 28 March–1 April 1976. Documenta Ophthalmologica Proceedings Series No. 9, Pp. 369, 360+3 coloured figs., and 38 tables, refs. W. Junk: The Hague (Dtch. Glds. 180)

Most leading authorities on the diagnosis and treatment of retinal diseases other than retinal detachment due to retinal hole attended this international symposium on fluorescein angiography in Ghent and presented papers. The important feature of the meeting was the free discussion. Within seven months the proceedings together with the discussions in full have been published. To have done this within so short a period must evoke admiration for the editor, Dr de Laey, and the publishers. The book is fully illustrated and the discussions make lively reading. There are authoritative accounts of the instrumentation and technique of fluorescein angiography, and these are followed by contributions on the retina, choroidal circulation, choroidal disease, and diseases affecting the pigment epithelium. Many of the important advances during the last few years are reported. While some of the papers may not be totally original, it is very valuable for all workers interested in retinal disease to have them collected in a single volume. The opinions expressed in the discussions contain unpublished observations and are most valuable in that the impact of the papers on such an audience has been recorded. This book represents an important contribution to the published material on retinal diseases. ALAN BIRD

Ocular Examination: Basis and Technique. 2nd ed. By A. H. Keeney. 1976. Pp. 322, 200 figs., tables, refs. C. V. Mosby: St. Louis (£17·50)

The second edition of this volume maintains the high standards of its predecessor. The methods of ocular examination together with their accompanying instrumentation and techniques are described in detail. The book remains objective in its discussion and the advantages and disadvantages of the various procedures are evaluated. Nor does the discussion confine itself to a description of contemporary instruments. There are frequent references to the disease processes that form the subjects of examination and there is much useful clinical advice.

British ophthalmologists may find the opening chapter on equipping an examination room amusing for its counsel of excellence, but the subject is approached with good commonsense and logic. There are valuable chapters on the examination of the pupils and on the diagnosis and investigation of dyslexia. The book is likely to appeal not only to the postgraduate student anxious to acquaint himself with modern instruments and diagnostic techniques but also to the practising ophthalmologist wishing to keep up to date with recent technical advances. T. J. FFYTCHE

Correspondence

A simple technique for photographing living microfilariae of *Onchocerca volvulus* in the anterior chamber of the eye

TO THE EDITOR, *British Journal of Ophthalmology*

SIR, Living microfilariae in the anterior chamber of the eye are a common sign of ocular onchocerciasis, but so far there has been no known technique for photographing them. A microfilaria in the corneal stroma was photographed with a retroillumination technique by Brown (1971), but the living microfilariae in the anterior chamber present a problem because of their mobility. Sarkies (1951) observed that the microfilariae in the anterior chamber could be seen with an ophthalmoscope in the light reflected from the fundus.

It is possible to take photographs of the microfilariae in the anterior chamber with the fundus reflex as background and using a Kowa RC-2 camera. The media of the eye must be perfectly clear and the pupil well dilated. Also, the camera must be held in a position where the optic disc will be in line to give a luminous fundus reflex. The patient should have his head bent down before the examination, as described by Anderson and Fuglsang (1973), to make the maximum number of microfilariae visible in the central anterior chamber close to the cornea. This facilitates focusing with the camera. The camera lens with magnification ×2 was used at the closest possible distance from the eye. Exposure with Kodachrome 64 reversal film was made at intensity step 6 of the electronic flash.

The technique described above can be used under field conditions and is of interest for education purposes.

Yours faithfully,
B. THYLEFORS

Onchocerciasis Control Programme in the
Volta River Basin Area
OMS/OCP BP 549
Ouagadougou,
Upper Volta

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Obituary

F. T. Ridley, MSc, MB, BS, FRCS

Mr F. T. Ridley, formerly surgeon to Moorfields Eye Hospital, died on 2 February. He was 73.

Frederick Thomas Ridley was born in Birmingham and received his early education at King Edward's school. He graduated B.Sc. Birmingham in 1922 and proceeded M.B., B.S. London in 1925. He acquired the Fellowship of the Royal College of Surgeons in 1928.

In his early days at St Mary's Hospital he worked with Fleming on lysozyme and devised a method of purification and concentration. Later, after the discovery of penicillin by Fleming, Ridley's method was applied to this new substance, and he was the first to show that penicillin would go into solution in an organic solvent such as alcohol and that it was possible to get rid of inert and possibly toxic material in this way.

In 1948 he was appointed to Moorfields Eye Hospital from the Central Eye Hospital in Judd Street, where he was surgeon and one time pathologist. He set up at High Holborn the contact lens department, which became an active centre for research on the role of contact lenses in the treatment of eye disease. He was president of the Section of Ophthalmology at the Royal Society of Medicine in 1963, and he was honoured by the Middlemore lectureship in 1951, the Doyne memorial medal in 1954, the Edward Nettleship prize and gold medal in 1953, and the Sight Foundation Award of Baylor University in 1966.

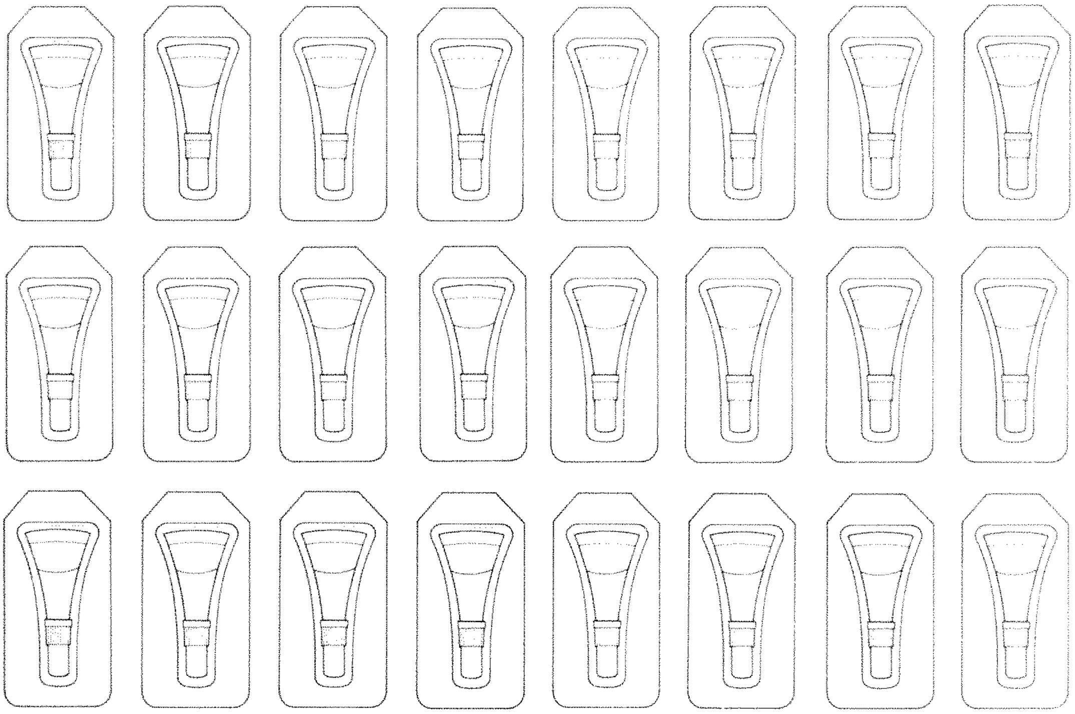
Frederick Ridley had a scientific outlook with an attraction for mathematics. It was for this reason he found the problems of contact lenses a satisfactory challenge as they appealed to his sense of accuracy. Purely clinical problems with their essential doubts and their inevitable irrelevancies rarely evoked his enthusiasm. His delight was abstract discussion. As senior surgeon at Moorfields Eye Hospital, High Holborn, he made himself available to any member of the staff who was in difficulties or needed his help. He would readily champion a cause, especially if it were in danger of being lost, or an individual, particularly if there was a suggestion of deprivation of rights. In action his big-heartedness could always be relied upon, for beneath his philosophical musings he hid a kindly and considerate personality. He is survived by his wife, Pauline Cartier Bourgeois, and two daughters by his previous marriage, Diana and Sandra, and by two grandchildren.

Notes

Canadian Ophthalmological Society

Calgary, 5–9 June

The 40th annual meeting will be held at the Calgary Convention Centre in Calgary, Alberta, on 5–9 June. The programme will include feature symposia on orbital diseases and on recent advances in ophthalmology, as well as 10 clinical workshops (a new departure) and selected free papers. Further information and registration forms from the Canadian Ophthalmological Society, PO Box 8650, Ottawa, Ontario K1G 0G8, Canada (tel. (613) 731-6493).



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The International Society of Geographical Ophthalmology will hold its next meeting in Cagliari Sardinia under the Chairmanship of Professor Orzalesi. Papers are invited for presentation with an emphasis on the geographic nature and distribution of the various ocular manifestations. The papers may be presented either in the Symposia or Workshops.

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NOTICE

ROYAL COLLEGE OF SURGEONS IN IRELAND POSTGRADUATE COURSE IN OPHTHALMOLOGY

There will be a two-week Intensive Course in preparation for the Diploma in Ophthalmology Examination at this College commencing Monday 12th September 1977. The Fee is: £50. The Examination commences 26th September. Further particulars may be obtained from: The Registrar, The Royal College of Surgeons in Ireland, 123 St. Stephen's Green, Dublin 2.

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The author should make adequate reference to previous work on his subject, and provide a full summary of his observations and conclusions.

Articles must be typewritten on one side of the paper only, in double spacing with ample margins. Only recognised abbreviations should be used. Authors are asked to submit two copies of the text and references.

ILLUSTRATIONS These should be marked on the back with the author's name and the top edge indicated. The author is advised to send prints of *x*-ray films which bring out the exact points to be illustrated. Photographs should be printed on glossy paper, and should be a little larger than the size desired for reproduction. The magnification of photomicrographs should be given. Graphs, charts, and tables should be presented on separate sheets apart from the text. Except letters and numbers, which should be lightly written in pencil, diagrams should be drawn in black ink on white paper. Glossy prints of diagrams should not be submitted.

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> Snodgrass, M. B. (1976). Ocular findings in a case of fucosidosis. *British Journal of Ophthalmology*, **60**, 508-511.

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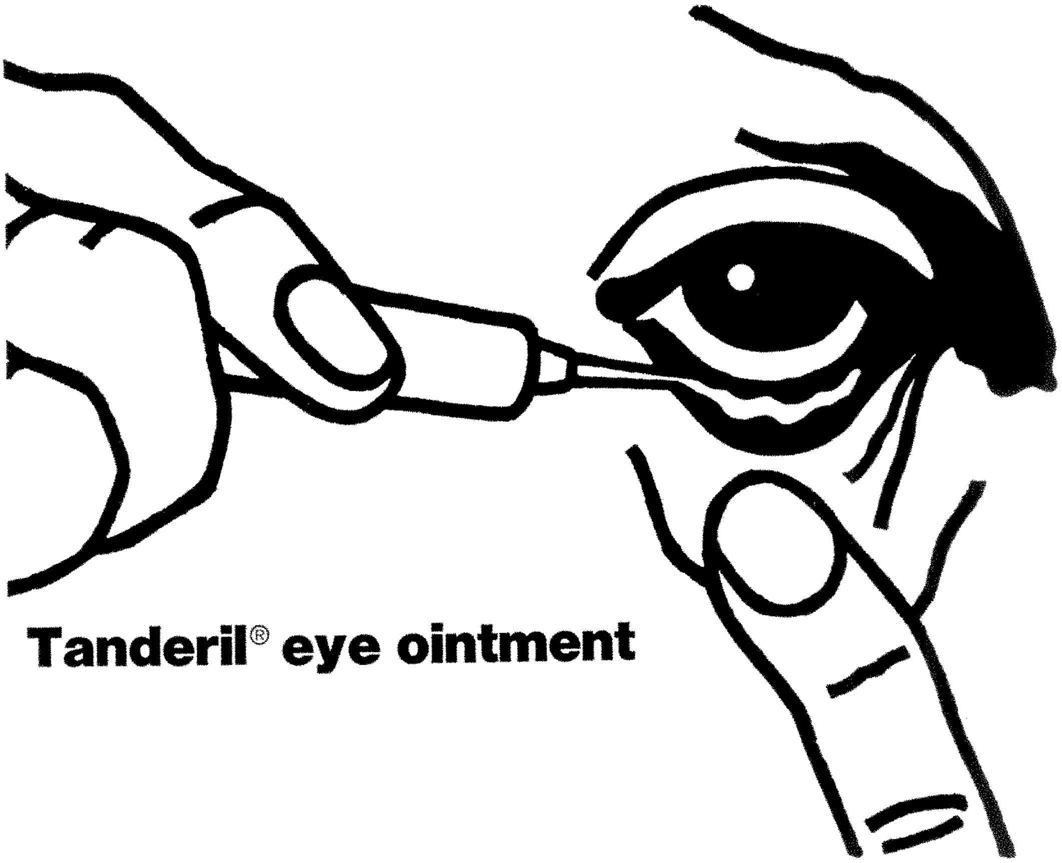

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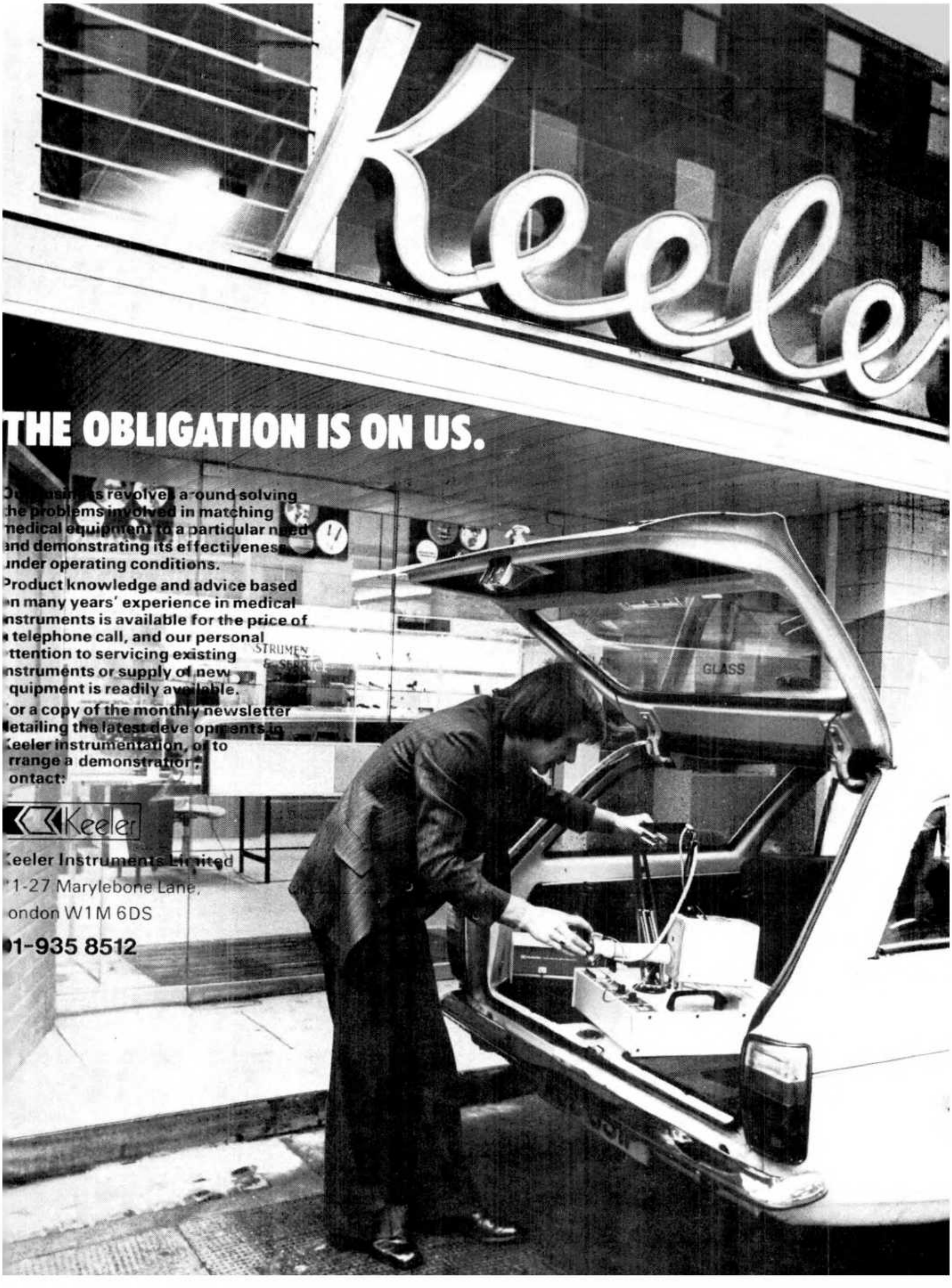

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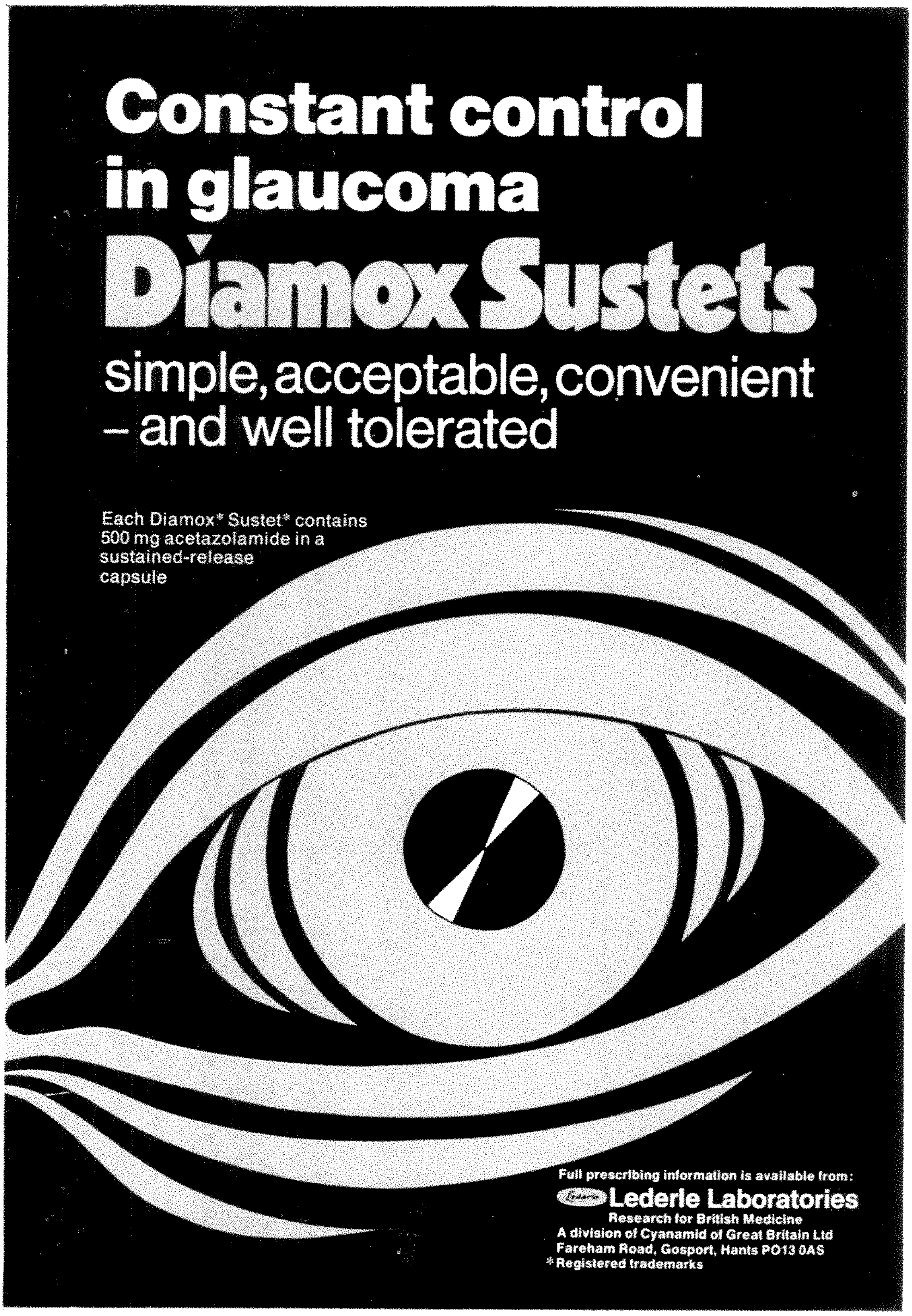

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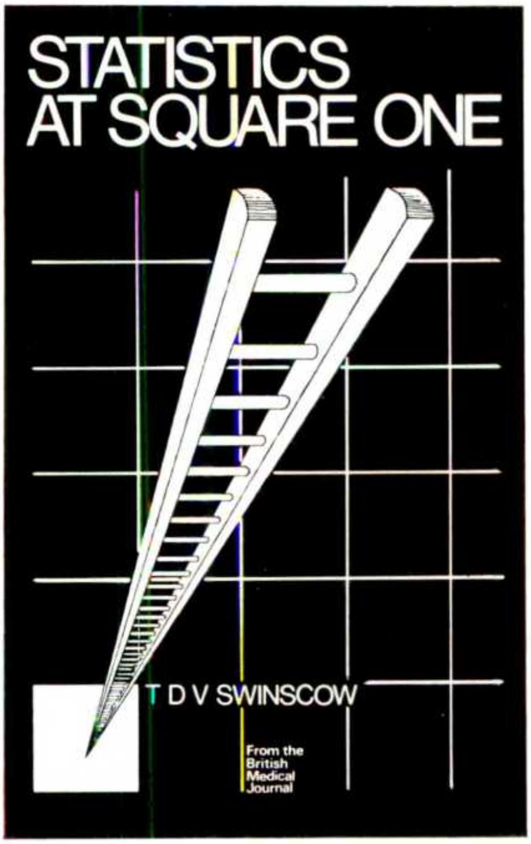

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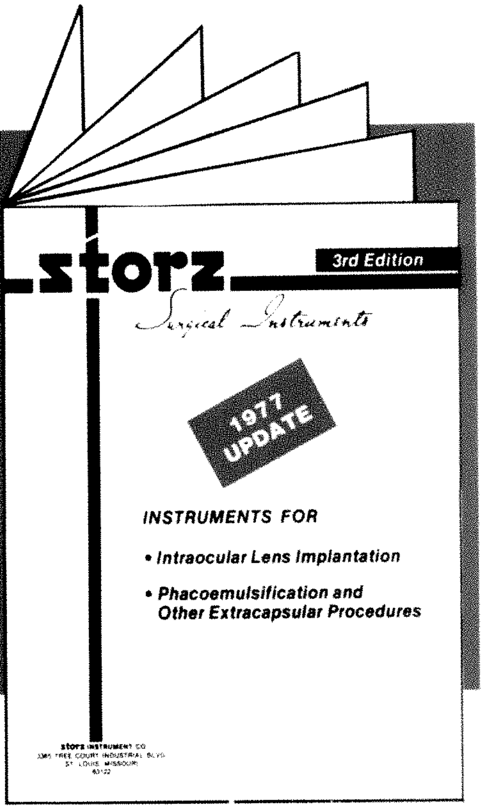

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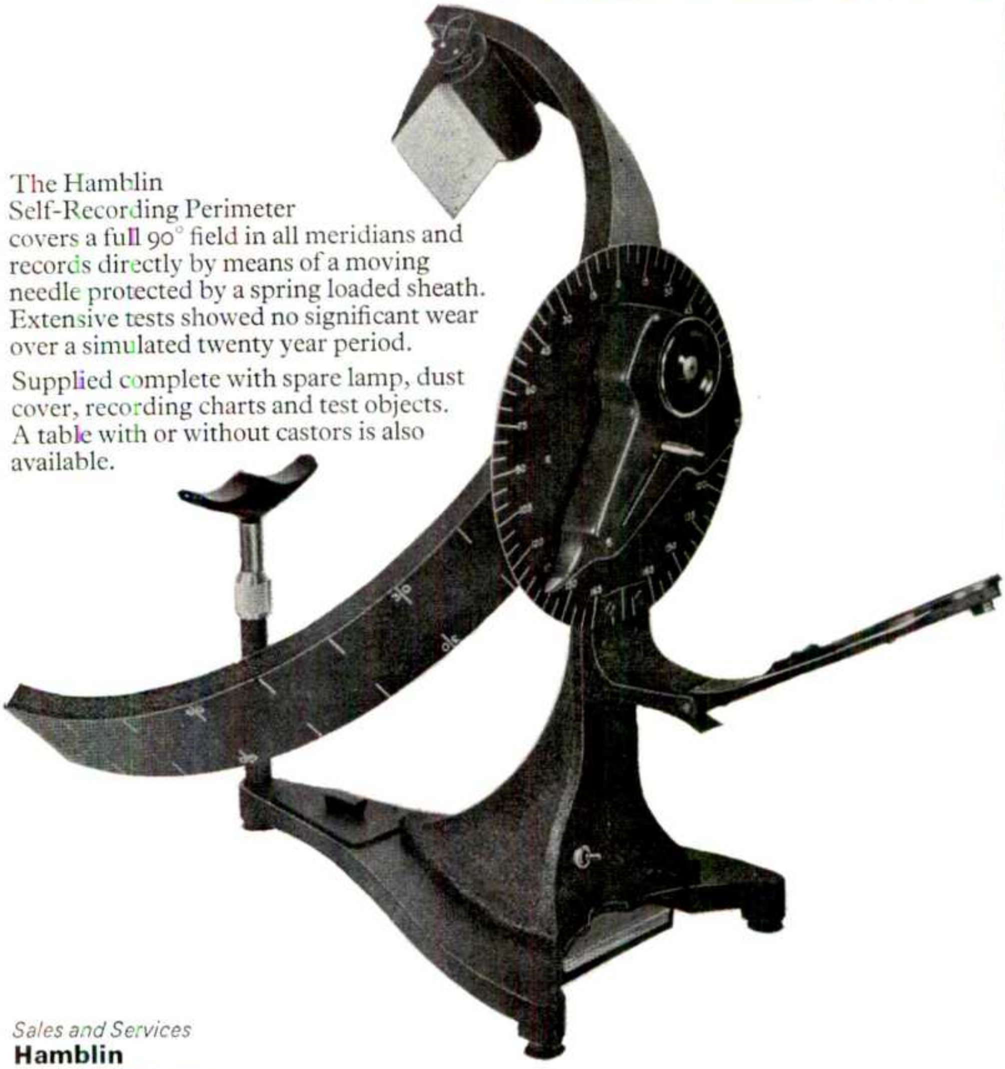

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Editorial: The case against the lens

It is well known that after a perforating injury to the lens cataractous changes and inflammatory reactions follow in the traumatised eye. A similar inflammatory reaction may develop in the other eye at a later date, perhaps more violently if it harbours a cataract or is injured. In the past, especially before the steroid era, when extracapsular lens extraction was a common procedure, the incidence of lens-induced uveitis was high. The involvement of the unoperated eye after this procedure was first noted by Straub (1919), and this phenomenon was later well documented by, among others, Courtney (1942), Irvine (1957), Witmer (1957), and Wirostko and Spalter (1967); in some cases, however, the superimposition of sympathetic ophthalmitis could not be ruled out. It is of interest that Easom and Zimmerman (1964), in a report of 7 cases, noted that whereas the exciting eye showed the picture of sympathetic ophthalmitis the sympathising eye had lesions of both sympathetic ophthalmitis and phacoanaphylaxis in 6 cases; in further 4 cases in which the exciting eye could not be examined the so-called sympathising eye showed only phacoanaphylaxis histologically. Blodi (1959) believes that hypersensitivity to lens proteins may play some part in the causation of sympathetic ophthalmitis.

Since planned extracapsular extraction is rarely undertaken in the Western world, the incidence of postoperative lens-induced uveitis has declined sharply, but it is still a daunting problem in the developing world, where not only is the incidence of cataract high but it also occurs at a much earlier age, and owing to socioeconomic reasons and manpower problems a large number of lenses are removed by the extracapsular method. There has been renewed interest in this problem because of the increased incidence of ocular injury due to road traffic accidents. A failure by ophthalmologists to treat such cases more drastically and to remove the injured lens at the time of wound repair may lead to clinically unsuspected phacoanaphylaxis (Perlman and Albert, 1977). If the other eye is injured or operated on at a later date, a violent lens-induced inflammation may develop.

In the past 3 distinct types of lens-induced ocular inflammation were recognised. The first was a severe form called endophthalmitis phacoanaphylactica or phacogenic uveitis; it showed an initial polymorphonuclear infiltration which later developed a granulomatous reaction characterised by palisading mononuclear phagocytes, epithelioid cells, and giant cells. The second was a less severe form called 'phacotoxic uveitis', which showed features of a mainly non-granulomatous inflammation. The third was phacolytic glaucoma, in which liquefied lens protein from a hypermature cataract attracted a large number of phagocytic mononuclear cells which blocked the filtration angle, leading to a raised intraocular pressure. Phacolytic glaucoma is now considered to be a non-immune phenomenon and there is no evidence that lens protein is toxic. Since anaphylaxis is now used to signify a special class of allergic reaction mediated by IgE, the term endophthalmitis phacoanaphylactica has a limited use. Rahi *et al.* (1977) have suggested that the condition be called phacoallergic endophthalmitis, in which the inflammatory process involves not only the uvea but also the lens and the vitreous and which can be produced by both antibody as well as T-cell mediated hypersensitivity reactions (Marak *et al.*, 1976; Kincses and Szabo 1976).

It should be realised, however, that the evidence that autologous lens proteins are involved in ocular allergic reactions has so far been indirect. Since the first demonstration that heterologous lens proteins are antigenic (Uhlenhuth, 1903) experiments have been carried out to establish that an immune reaction to lens proteins may lead to ocular inflammation. These studies have been carried out, however, with either xenogeneic (Verhoeff and Lemoine, 1922), allogeneic (Goodner, 1964) or syngeneic (Behrens and Manski, 1973) material, and although antilens antibodies have been detected in lens-induced uveitis in man (Wirostko and Spalter, 1967) there has been no evidence so far that autologous lens proteins are antigenic. In this issue of the journal Rahi, Misra, and Morgan (p. 371) show for the first time that not only are autologous lens proteins antigenic but they stimulate both B- and T-lymphocyte activity. The allergic response in their animals was variable, however, suggesting a modulatory role played by the immune response genes which are believed to be linked to the major histocompatibility system. Thus every ocular injury does not lead to an autoimmune inflammation; in fact only about a quarter of the patients develop uveal inflammation of any degree after unplanned extracapsular extraction.

Since it is now known that soluble lens proteins may be present in small amounts even in the aqueous humour of individuals with normal lenses (Sandberg, 1976), it would be interesting and valuable to examine preoperative blood specimens from patients with cataracts for evidence of lens haemagglutinating antibody and T-cell sensitisation —these immunological tests according to Rahi *et al.* (1977) appear to be the most reliable indicators of lens allergy—and to see if the individuals with positive tests are more likely to develop postoperative complications. This information would be essential in anticipation of an uncomplicated lensectomy.

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Immunopathology of the lens

III. Humoral and cellular immune responses to autologous lens antigens and their roles in ocular inflammation

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SUMMARY In experimental rabbits it has been shown for the first time that autologous lens protein is antigenic when injected with Freund's complete adjuvant. Although lens haemagglutinins were detected in 6 out of 7 rabbits, in only 3 of the 6 animals did the titre reach a maximum of 1:640. A weak agar precipitation reaction was obtained with only 1 of the 3 sera. It would appear, therefore, that the passive haemagglutination test is superior for the detection of autologous lens antibodies.

The response to autologous lens antigens both in magnitude as well as in duration varied in different rabbits, which suggested to us the possible role played by a central control mechanism involving the immune-response (Ir) and immune-associated (Ia) genes which are part of the major histocompatibility complex. Alternatively, this variation may be the result of an antigenic competition between various autologous crystallins.

Antibodies to autologous lens protein as detected by immunofluorescence and immunoperoxidase techniques were shown to be of the IgG class. Systemic autologous immunisation produces only a mild uveitis and does not lead to a granulomatous intraocular inflammation. Intravitreal injections of autologous lens protein in pre-immunised animals, however, produced an Arthus type of acute endophthalmitis. Autologous lens antisera showed limited cross-reactivity with ocular and extraocular tissues, which could be detected only by such sensitive techniques as immunofluorescence and immunoperoxidase methods.

Uhlenhuth (1903) showed that rabbits could be immunised by repeated intravenous injections of bovine lens and that their sera showed positive precipitation reactions with lens proteins from other animals. It was well known at that time that injury to the lens in human beings might in some cases be followed by an inflammatory reaction. Verhoeff and Lemoine (1922), encouraged by these findings of Uhlenhuth, proposed that this 'endophthalmitis phako-anaphylactica' (the original term used by Straub (1919) was endophthalmitis phakogenetica) may depend upon some form of hypersensitivity to lens proteins. They strengthened this hypothesis by experiments in guinea-pigs and rabbits in which pre-immunisation with heterologous lens protein followed by discission of the lens led to an intraocular inflammation. This reaction was produced, however, after the combination of autologous antigens from the ruptured lens with antibodies produced against heterologous lens protein. It cannot be regarded, therefore, as a true autoimmune reaction, in which it is essential that the autologous lens should also act as the immunising antigen. In a later study Manski *et al.* (1965) claimed to have induced lens autoantibody production in rabbits by heterologous and homologous immunisation, because in their study the antiserum thus produced reacted *in vitro* with lenses obtained from the immunised animals. Clearly, this is a well-known phenomenon of cross-reactivity, and unless an antiserum is raised against autologous lens antigen the antibodies reactive with these proteins *in vitro* cannot be regarded as true autoantibodies.

In a recent study Behrens and Manski (1973) immunised inbred rats with homologous lens proteins from litter mates and obtained an antibody response to α-crystallins. Since the animals used were inbred, the authors argue that this may be regarded as equivalent to autoimmunisation. Although there may not be any appreciable differences

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in the nature of immune responses, the results of such experiments also cannot be regarded as true autoimmunity.

The present work was undertaken, therefore, to study both humoral and cellular immune responses to autologous lens proteins in rabbits. Although agar gel diffusion, immunoelectrophoresis, and passive haemagglutination techniques have been used widely to test homologous and heterologous lens antibody responses, and although data are now available on other sophisticated techniques such as immunofluorescence and immunoperoxidase methods (Misra *et al.*, 1977; Rahi *et al.*, 1977), it is not known which technique is best suited for the diagnosis of phakoallergic endophthalmitis* in man and experimental animals. Morover, the class of antibody involved in this autoimmune reaction is unknown. Although it has been suggested that lens-induced uveitis is primarily an immune-complex disease (Marak *et al.*, 1976), it has also been claimed that a cellular hypersensitivity reaction plays an important pathogenetic role (Kincses and Szabo, 1976). Since studies have not been performed on experimental animals to examine critically the role of both B and T lymphocytes in an immune response to autologous lens protein, the nature of the lesion in clinical practice remains in dispute. Furthermore, although the cross-reactivity of heterologous lens antisera with various other ocular and extraocular tissues is well documented, it is still unknown if lens autoantibodies similarly show a degree of non-specificity.

Methods and materials

The experiments were performed on 7 New Zealand albino adult rabbits using litter mates where possible. Extracapsular lens extraction was performed on 1 eye under sodium pentobarbitone anaesthesia using a standard technique and a dissecting microscope, after which some lens matter remained *in situ*. The lenses were homogenised separately, divided into aliquots, and stored frozen. Each rabbit received 4 intramuscular injections of autologous lens in Freund's complete adjuvant at 10-day intervals. They were bled on the day of initial immunisation and also at the time of subsequent injections to study the sequential antibody response. The serum specimens were also deep frozen in aliquots. After the fourth immunising dose (i.e., 30 days) the animals were skin-tested and the sites biopsied 48 hours later. In 2 preimmunised animals 0·05 ml of autologous lens material was injected intravitreally into the operated eye. All the animals were killed 10 days after the last immunising dose, and blood was collected from the heart in preservative-free heparinised containers for lymphocyte transformation tests. Both eyes were enucleated for microscopical examination. One control group of rabbits received intramuscular injections of Freund's complete adjuvant only, and blood was tested for evidence of humoral and cellular immunity to lens protein. In another group of rabbits not previously immunised 0·05 ml of autologous lens material was injected into the vitreous of 1 eye, and both eyes were examined histologically 1 week later for any evidence of inflammation.

Immunological investigations

The *Ouchterlony test* was performed on glass plates coated with 1·5% agar in barbitone buffer (pH 8·2). The plates were kept at 4°C for 1 week and then washed in 3% saline and later in distilled water. After air-drying they were stained with 1% nigrosine.

Immunoelectrophoresis and Osserman tests were performed on similar glass plates coated with 1·5% agar in barbitone buffer (pH 8·2; I=0·05). The electrode compartments of the electrophoresis tank were filled with barbitone buffer pH 8·6 (I=0·075). The electrophoresis was carried out at a constant current (10 mA/plate) for 3 hours according to the method described previously (Rahi and Chignell, 1975).

Passive haemagglutination test.—The technique used was essentially the same as described previously (Rahi *et al.*, 1977). The volume of tanned red cells coated with antigen was modified according to the availability of autologous lens protein. The test was performed on a microtitre assay system (Cooke Laboratory). Sera from immunised and control animals were heat-inactivated and preadsorbed with unsensitised sheep red cells. Proper controls were set up with sensitised cells in buffer alone and with non-immune serum obtained from the animals before initial immunisation. Controls were also set up using unsensitised cells with and without antiserum.

The indirect immunofluorescence test. was performed using a standard technique. A Zeiss epifluorescence microscope equipped with an interference filter was used for the present study. Frozen sections of a composite block consisting of liver, kidney, stomach, parotid, and diaphragm from a rat and stomach from a mouse were used to detect cross-reacting antibodies in autologous antilens sera. Rabbit, guinea-pig, and rat eye sections were used to detect immune reactions not only with the lens but also with other ocular structures. The sera were tested at an initial dilution of 1:2 and both polyvalent (Wellcome) and IgG specific (Dako) anti-rabbit immunoglobulin labelled with fluorescein were used for the present study.

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*The term phakoallergic endophthalmitis has been used throughout the text as a preferred alternative to such terms as lens-induced uveitis, endophthalmitis phakoanaphylactica, or phakogenetic endophthalmitis. The reasons for this are discussed in a separate communication.

The immunoperoxidase test.—Frozen sections of the composite block and of the eyes, similar to those required for immunofluorescence study, were used for immunoperoxidase staining. The sera were tested at the initial dilution of 1:2 and the technique was essentially the same as described previously (Rahi *et al.*, 1977).

The lymphocyte transformation test.—10^6 lymphocytes separated from the blood of the immunised animals by the Ficoll-Hypaque technique were cultured in sterilised tubes containing 1 ml of medium 199, which was prepared in HEPES buffer. Antibiotics in the usual concentration were added to the medium, which was enriched by the addition of 10% fetal calf serum. 1 mg of autologous or homologous lens protein was added to each of the experimental tubes, and 48 hours later 2 μCi of tritiated thymidine (30 000 mCi/mmol) were added to both the control and the experimental tubes. After further incubation overnight at 37°C the tubes were centrifuged, and trichloracetic acid was added to the sediment to precipitate the proteins. These were filtered on glassfibre filter-paper and washed in methanol. The filter-papers were then transferred to scintillation vials and air-dried. The radioactivity was measured in a Packard tricarb liquid scintillation counter after the addition of 10 ml of toluene-based scintillation fluid.

Results

Blood collected from rabbits before immunisation was negative for lens antibodies.

Antibodies to autologous lens protein injected with Freund's complete adjuvant were detectable by the passive haemagglutination test in 2 rabbits on the 10th day of immunisation. In 4 others it was delayed for several more days and in 1 rabbit no antibody was detected even after 40 days (Fig. 1; Tables 1 and 2).

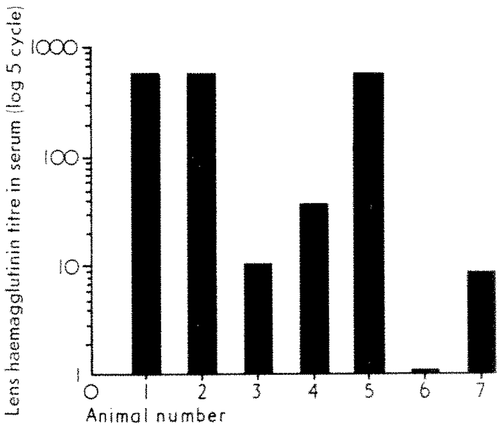

Fig. 1 *Biological variations in antibody response in a group of 7 rabbits injected with autologous whole-lens protein in Freund's complete adjuvant, 40 days after regular immunisation at 10-day intervals*

Table 1 *Antibody response in a rabbit injected with autologous whole-lens homogenate in Freund's complete adjuvant*

Methods of antibody detection	*Days after initial immunisation*			
	10	*20*	*30*	*40*
Gel diffusion (Ouchterlony)	–	–	–	±
Immunoelectrophoresis	–	–	–	–
Passive haemagglutination	+ (1:10)	+ (1:40)	+ (1:160)	+ (1:640)
Indirect immunofluorescence	–	±	+	+
Immunoperoxidase	*	*	*	–

+ Positive, ± weak positive, – negative, * not tested

Table 2 *Antibody response in a group of rabbits injected with autologous lens protein in Freund's complete adjuvant; 40 days after regular immunisation at 10-day intervals*

Methods of antibody detection	*Rabbits studied*						
	No. 1	*No. 2*	*No. 3*	*No. 4*	*No. 5*	*No. 6*	*No. 7*
Gel diffusion (Ouchterlony)	–	±	–	–	–	–	–
Immunoelectrophoresis	–	–	–	–	–	–	–
Passive haemagglutination	+ (1:640)	+ (1:640)	+ (1:10)	+ (1:40)	+ (1:640)	– –	+ (1:10)
Indirect immunofluorescence	+	+	–	±	+	–	
Immunoperoxidase	+	+	*	*	*	–	*

+ Positive; ± weak positive; – negative; * not tested

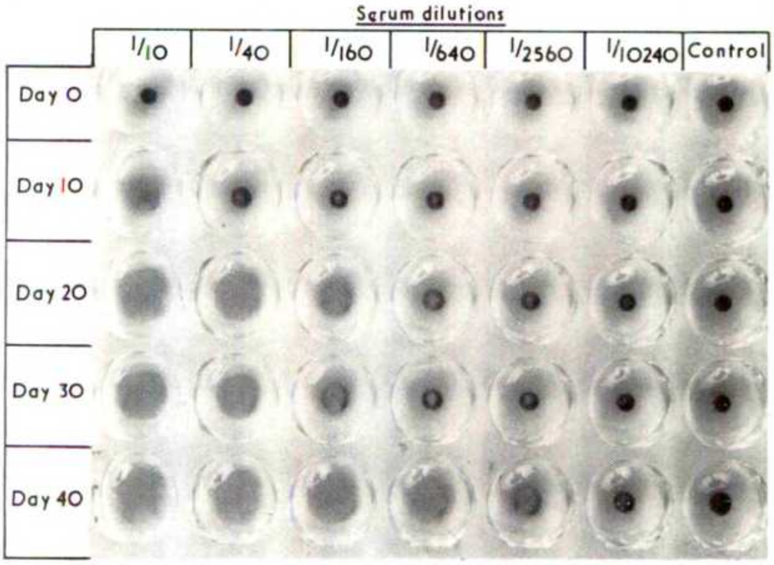

Fig. 2 *Passive haemagglutination test: Lens antibody titre in a rabbit before immunisation (i.e., day 0) and at 10, 20, 30, and 40 days after immunisation with autologous lens protein in Freund's complete adjuvant*

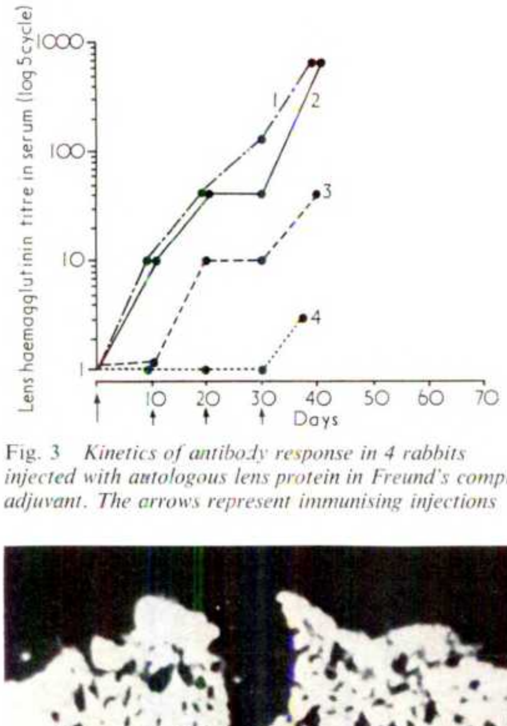

Fig. 3 *Kinetics of antibody response in 4 rabbits injected with autologous lens protein in Freund's complete adjuvant. The arrows represent immunising injections*

The final haemagglutinin titre 40 days after immunisation rose to 1:640 in 3 of the 7 rabbits.

A faint precipitin line was observed in the Ouchterlony plate with the serum from 1 rabbit and only after 40 days of regular immunisation. The haemagglutination titre in this rabbit at that time was 1:640 (Fig. 2).

The level of the immune response was subject to individual variation, and the kinetics of the antibody response to the autologous lens antigens are shown in Fig. 3.

The immunofluorescence and immunoperoxidase tests showed that the antilens sera reacted strongly with the lens epithelium and the outer cortex (Fig. 4). In addition sera with high lens haemagglutinin titre showed cross-reactivity with the iris (Fig. 5) and the corneal epithelium. A similar cross-reactivity, although of a relatively weak nature, was also observed with extraocular tissues such as smooth

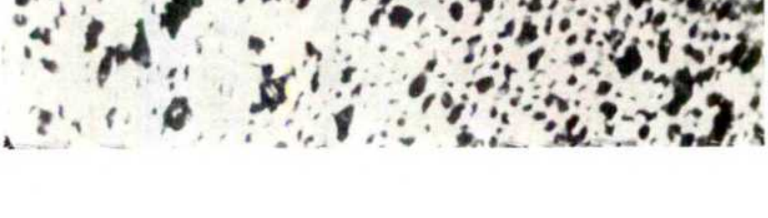

Fig. 4 *Indirect immunofluorescence test: The anti-lens serum contains IgG antibodies which react strongly with unfixed sections of rabbit lens.* ×480

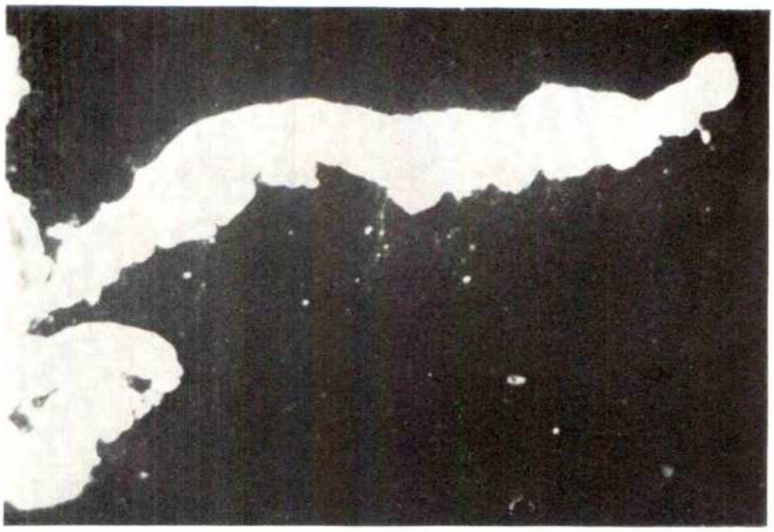

Fig. 5 *The iris of a rat showing bright fluorescence in the presence of lens antibody.* ×480

muscle fibres in the stomach, the hepatocytes and the renal tubules (Figs. 6 and 7) as previously described for heterologous and homologous antilens sera (Rahi *et al.*, 1977; Misra *et al.*, 1977).

The immunofluorescence and immunoperoxidase tests also showed that autologous lens antibodies belong to the IgG class. The possibility that they also belong to other classes of immunoglobulins, however, cannot be excluded.

Although the immunofluorescence and immunoperoxidase tests were positive with all those sera which contained haemagglutinating antibodies (>1:40), the immunofluorescence test being strongly positive when the lens haemagglutinin titres were 1:160 and above, the agar diffusion technique of Ouchterlony, in contrast, showed a weak positive result in 1 case when the haemagglutination titre was 1:640. The relative sensitivity of these *in vitro* techniques are shown in Table 2.

The lymphocyte transformation test was positive in only 3 of the 7 rabbits tested. The level of cellular hypersensitivity, however, was low (mean lymphocyte transformation index = 2·15) but correlated well with the lens haemagglutinin titre in the serum.

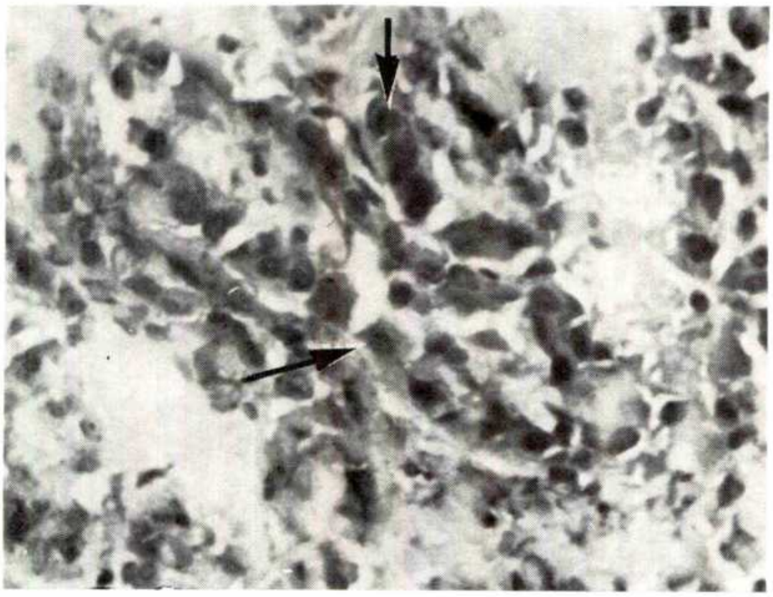

Fig. 6 *Indirect immunoperoxidase test: The lens antiserum reacts with the cytoplasm* (arrows) *of the tubular epithelium of a rat kidney, suggesting the presence of mitochondrial and ribosomal antibodies. The nuclei have been counterstained with haematoxylin.* ×900

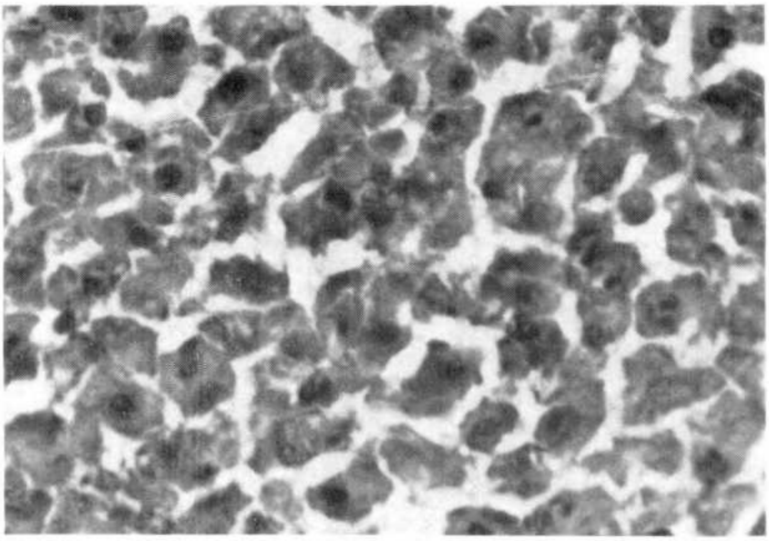

Fig. 7 *Sections of a rat liver showing a positive immunoperoxidase test. The lens antiserum seems to contain antibodies which react with the cytoplasmic organelles (e.g., mitochondria and ribosomes) of the hepatocytes. The nuclei have been counterstained with haematoxylin.* ×900

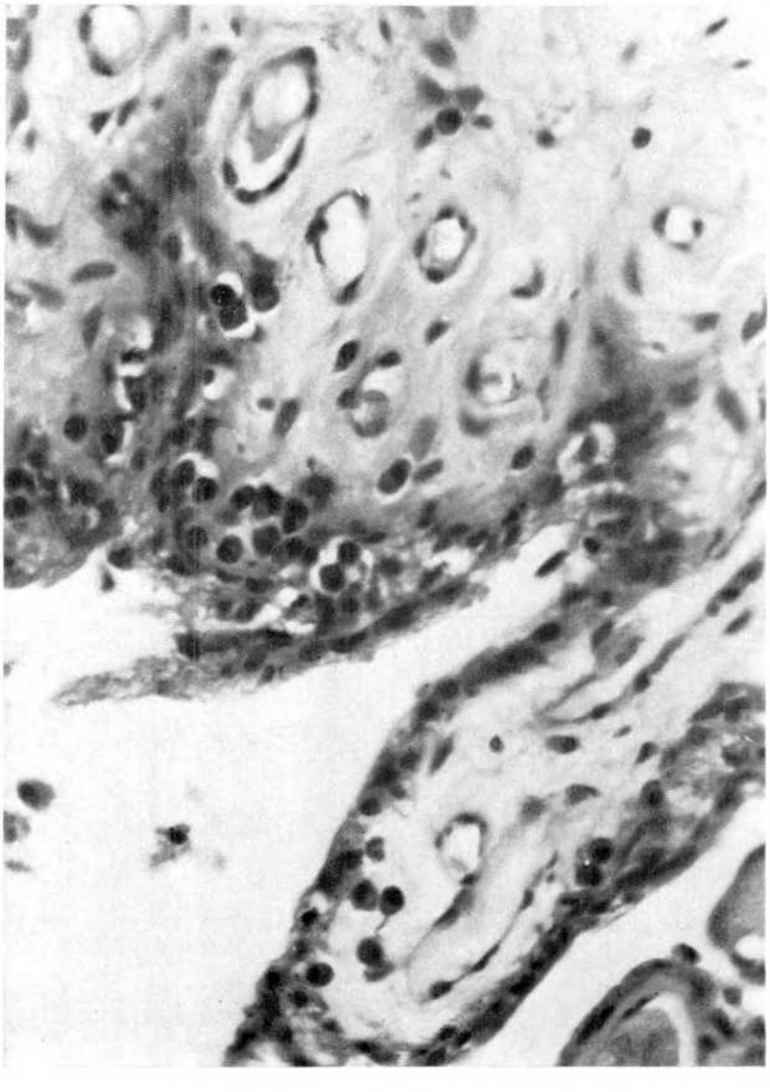

Fig. 8 *The iris and ciliary body of an immune rabbit show infiltration by a small number of lymphocytes and plasma cells. H and E.* ×900

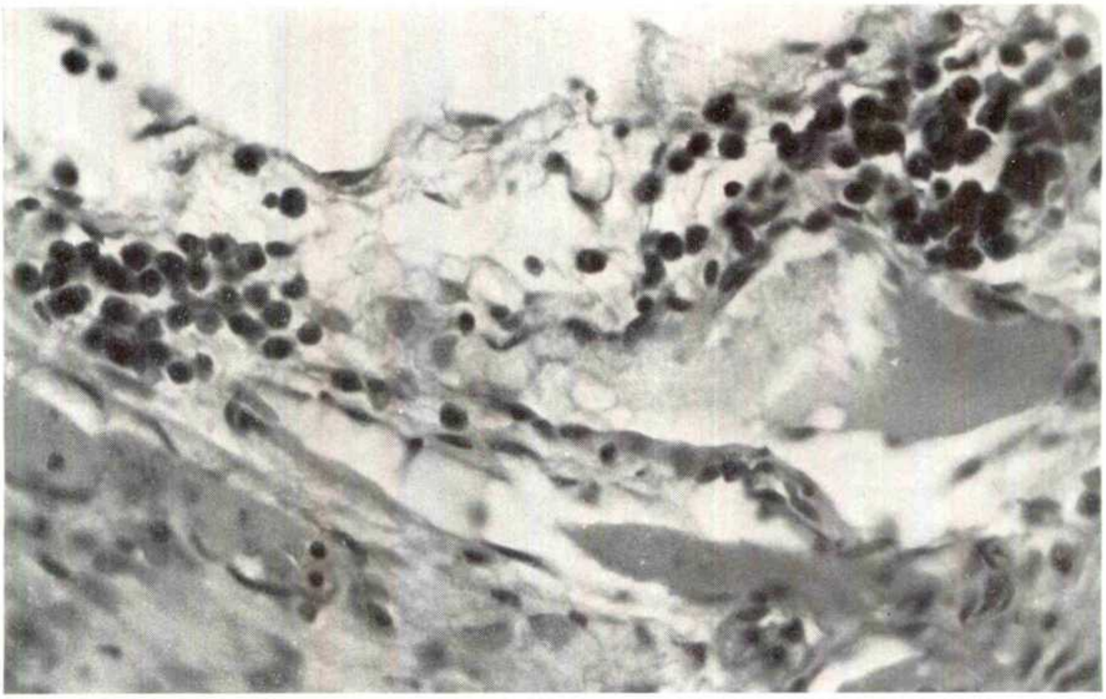

Fig. 9 *The choroid from the same rabbit immunised with autologous lens in complete Freund's adjuvant shows lymphocytic and plasma cell infiltration. H and E.* × 900

Histological examination of the eyes from immunised rabbits showed occasional lymphocytes and plasma cells in the iris, the ciliary body and the choroid (Figs. 8 and 9). There was evidence of subcapsular fibrosis in the lens remnants (Fig. 10), which were surrounded by lens-protein-containing macrophages (Fig. 11). In 2 preimmunised rabbits in which autologous lens extract was injected into the vitreous a hypopyon was present in the anterior chamber, and the lens remnants were surrounded by neutrophils, which were also seen in the vitreous and the retina. There was no evidence of a granulomatous reaction in any of the eyes, but there were a few large macrophages which contained nuclear debris in the anterior chamber (Fig. 12).

Discussion

The present study has shown for the first time that animals can be immunised against their own lens proteins, thus supporting the idea that autoimmunisation may lead to intraocular inflammation. The antibody response on the 40th day (i.e., after the fourth and final injection), however, was much weaker than that to heterologous lens antigens for the same period of immunisation (Rahi *et al.*, 1977). A similar weak response to homologous lens proteins was observed during the early weeks of immunisation, the antibody titre reaching a peak only after 3 months (Misra *et al.*, 1977).

In 1 rabbit only a precipitating antibody was present which was probably against the more strongly antigenic α-crystallin. In the remaining animals antibodies were detected only by the much more sensitive haemagglutination technique (concentration of the serum or separation of the globulins from the other serum proteins was not attempted). It is possible that if this is done in future experiments the agar-gel immunoelectrophoretic methods may provide a better insight into the antigenic components of the autologous lens proteins.

Since it has been shown that the maximum haemagglutinin titre on the 40th day of immunisation using heterologous lens in Freund's complete adjuvant is 1:10 240 (Rahi *et al.*, 1977) as compared with a 1:640 titre obtained with either homologous (Misra *et al.*, 1977) or autologous lenses, it now seems certain that heterologous lens proteins are much more strongly antigenic than either homologous or autologous lens antigens. Furthermore, the haemagglutinin titre to autologous lens proteins, even when injected with Freund's complete adjuvant, never went higher (and, in fact, in some animals remained much lower) than the antibody response

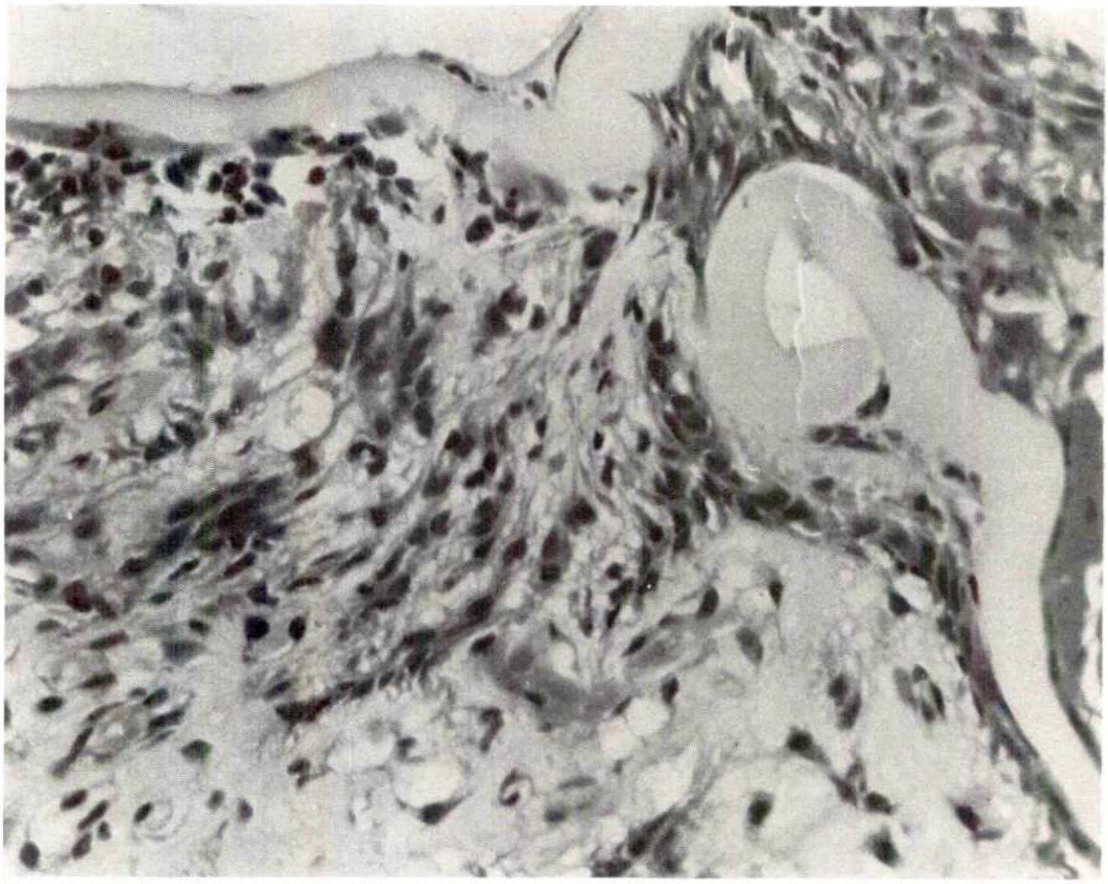

Fig. 10 *The lens remnants of a rabbit immunised with autologous lens in complete Freund's adjuvant show lymphocytic infiltration and subcapsular fibrosis. H and E.* × 900

to heterologous lens protein when injected without any adjuvant.

It is possible, however, that there are no real differences in the antigenicity of the various lenses but that the rabbits show a degree of immune unresponsiveness to lens proteins which can be overcome only with the addition of strong adjuvant when autologous antigen is used. In contrast, this tolerance seems to break down much more easily even when small doses of heterologous lens proteins are injected. In this situation adjuvant is required only when it is desirable to produce an accelerated immune response with a high antibody titre.

Since the antibody titre in 4 out of 7 rabbits remained very low even after 40 days of immunisation, it seems unlikely that animals will respond to autologous lens proteins when given without adjuvant unless injected in large doses, which is not possible for obvious reasons. This aspect of lens immunology is being investigated and will be reported at a later date.

In contrast to humoral responses, however, a complete Freund's adjuvant is required for a good cell-mediated immune response to lens protein irrespective of whether the antigens are auto-, homo-, or heterologous in nature.

The level of the antibody response to autologous lens protein varied in different animals, suggesting the possible role played by the immune-response (Ir) and immune-associated (Ia) genes, which are believed to control the immune reactivity of the lymphocytes of an individual to a variety of different antigens (Ellman *et al.*, 1970; Festenstein and Pena-Martinez, 1975; Munro and Taussig, 1975). Since in our study whole-lens homogenate rather than purified proteins was used for immunisation, it is possible that the variation in the immune response was due to the well-documented phenomenon of antigenic competition (Taussig *et al.*, 1973) between the molecules of the various crystallins. Furthermore, it is also possible that the variability of the

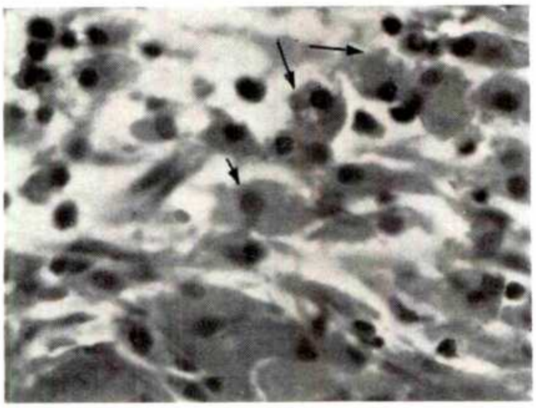

Fig. 11 *Macrophages* (arrows) *and lymphocytes surround lens remnants in a rabbit immunised with autologous lens proteins in Freund's complete adjuvant. H and E.* × 900

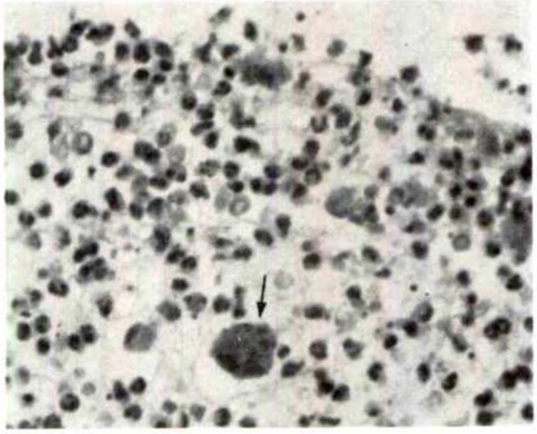

Fig. 12 *The anterior chamber of an immunised rabbit 24 hours after an intraocular injection of autologous lens homogenate, showing a large number of neutrophils and a few macrophages which contain nuclear debris.* × 900

response to lens antigens is not due to tolerance or antigenic competition but to another phenomenon in which T lymphocytes act as suppressor cells (Weber and Kolsch, 1973).

The immunofluorescence and immunoperoxidase tests used in this study have the one advantage over the haemagglutination test in being able to detect the chemical class of the immunoglobulins involved in an immune reaction. It has been possible, therefore, to state with certainty that IgG is involved in autologous lens antibody reactions. This does not exclude, however, the possible role of other immunoglobulins.

Systemic immunisation with autologous lens protein did not lead to a granulomatous inflammatory reaction either in the uvea or in and around the lens remnants. There was some evidence, however, of a mild immune reaction as evidenced by the infiltration of the anterior uvea by a small number of lymphocytes and plasma cells and the presence of macrophages in the region of lens remnants. Intravitreal injections of autologous lens proteins in preimmunised animals led to marked polymorphonuclear infiltration suggesting an Arthus type of reaction. In addition there were a few large histiocytes which contained nuclear debris.

Since in the present study only soluble lens proteins were used and in relatively small doses, it is possible that the rabbits were not sufficiently sensitised to manifest a granulomatous reaction, which is a common histological feature of a delayed hypersensitivity reaction. That this is the case is supported by the fact that the animals in the present series did not show a marked lymphoblastic change when challenged *in vitro* with autologous lens antigen.

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Cataracts and avionic radiations

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SUMMARY Nine cases of hertzian radiation cataracts are reported among personnel working in operational aviation environments, where they were irradiated repeatedly at subliminal nonthermal field intensities. The resultant ocular pathology evolved insidiously and slowly over a period of years in a similar way to other forms of radiational injury. By the time of consultation examination, all had progressed to a relatively late state, exhibiting not only capsular cataract but also vesiculation and opacification of the proximal subcapsular lens substance.

In addition to the ocular dangers of chronic exposure to nonionising radiation reference is made to the nonthermal effect or the radiation effect *per se*, as this could relate to general health—for example, as a possible previously unsuspected aetiological or contributory factor in many other disease processes.

Recently, high ambiences of stray nonionising radiation, vernacularly known as 'electronic smog', have been reported as a pervading air pollutant of importance (Bowers and Frey, 1972). Practically everyone in the general population is continuously or intermittently exposed—for example, from telecommunication networks—to field intensities greater than background levels of naturally occurring hertzian radiations (Tunney, 1973). The proceedings of the First International Symposium on the Biological Effects and Health Hazards of Microwave Radiation (Czerski, 1974) contain papers incriminating chronic exposure to hertzian radiation as an aetiological or contributory factor in neurophysiological, hormonal, haematopoietic, immunological, and cardiovascular dysfunction, teratogenesis, mutagenesis, and cataractogenesis.

The full significance of these findings has not yet become apparent to the medical community. With that aside, we will limit ourselves here to some ophthalmic aspects of this subject. First, we would call attention to a brilliantly prescient manuscript about cataractogenesis published more than 50 years ago (Duke-Elder, 1926). Sir Stewart showed that cumulative exposure to radiant energy, including long-term irradiation by sunlight, was the primary or sensitising aetiological factor for most types of cataract acquired during life. The data he presented indicated that rays originating anywhere throughout the electromagnetic radiation spectrum, from the longest wavelengths generated by electrical oscillations to the shortest wavelengths of ionising radiation, had the property of initiating cataract formation.

Here our attention will be limited to the wavelengths occupying the middle region of the nonionising portion of the spectrum, that is hertzian radiation, including microwaves and radiowaves. The lens opacities they produce are commonly referred to as microwave cataracts but more properly should be termed hertzian radiation cataracts.

Generally, the ubiquitous nature of electronic smog when coupled to the delayed appearance and slow evolution of signs and symptoms of hertzian radiation sickness present a formidable obstacle for the epidemiologist and militate against any immediate quantitative analysis in studying the hazards of electronic smog. Nevertheless, we can define qualitatively what are believed to be both a special population group at risk and an objective sign of injury by hertzian radiation.

The selected special population group at risk worked in operational aviation, where hertzian radiation has widespread applications in communication, navigation, and radar. For each individual in the cluster being reported, continuing good health was a requirement of the job, and all were obliged periodically to pass medical examinations which included a search for ocular disorders such as cataract and disturbed visual function.

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In the absence of history or findings suggestive of prior intraocular inflammatory disease capsular cataract, the sign used as our end point, is an unusual form of cataract in contrast to the ordinarily encountered forms of cataract occurring entirely within the lens substance itself. That microwave radiation may produce capsular cataract was (1) first reported in 1964 in 3 relatively young individuals who tested prototype microwave radiating devices (Zaret, 1964); (2) subsequently confirmed independently in a very young radar technician (Bouchat and Marsol, 1967); and (3) more recently reported in a middle-aged housewife who had used a consumer-type microwave oven for a period of 5 years (Zaret, 1974a).

One of us (M.M.Z.) was consulted about all the cases reported here and confirmed by slit-lamp biomicroscopy that far-advanced capsular cataract was present in at least 1 eye of each subject. Thus, these 9 patients had all worked for a long time in operational aviation environments containing stray hertzian radiation and all developed capsular cataract.

Case reports

Radar technicians. Three patients had been radar technicians who served as in-flight crew aboard EC121 (electronic intelligence) type aircraft. Case 1 was 35 years old when originally diagnosed as having cataracts. Case 2 was 48, and Case 3 was 35.

Air traffic controllers. Five patients had been air traffic controllers. Disturbance of visual function, which occasionally antedates the appearance of lens opacification, is described for 1 of the men. Case 4 was 50 years old when originally diagnosed as having cataracts. Case 5 was 39, case 6 was 52, and case 7 was 39. Case 8 was 48 years old when originally diagnosed as having incipient cataracts in 1970. However, his visual complaints began 3 years earlier, in 1967, with an episode of sudden obscuration of vision while actively controlling some 15 to 18 aircraft. The visual disturbance lasted for several hours. During the following 6 weeks 3 separate ophthalmological examinations, an extensive physical examination, and a neurological evaluation were performed, all without revealing any cause for the visual disturbance.

The patient continued to work as an air traffic controller between 1967 and 1972 despite similar sporadic recurrences of visual problems while at work. Each episode was followed by ophthalmic examinations, by which time visual acuity had improved and was then correctable to 20/20 for distance and Jaeger No. 1 print for near vision. On this basis he was continuously certified as being able to perform his duties as an air traffic controller despite the fact that potentially dangerous operational situations occurred on many occasions because of intermittently faulty vision. For example, while actively controlling 12 to 15 aircraft in 1971, without realising he could not see them on the radarscope, the patient lost the position and flight pattern of 2 military jet aircraft in his sector. Fortunately an associate controller noticed that the patient was having difficulty, recognised the danger, and intervened immediately.

Still other examples occurred in 1972 when on each of 2 successive shifts the patient wrongly identified 2 aircraft on the radarscope and in each instance unwittingly directed them into potential mid-air crash patterns. After these near-miss episodes the patient sought a change of job, and he was finally disqualified from working as an air traffic controller because of his difficulty with visual perception. At that time his visual acuity was correctable to 20/20 in the right eye and 20/30 in the left (where an incipient cataract had been known to be forming since 1970 but was not considered by the examiners to be disabling).

Airline pilot. Case 9 was a commercial airman having been certified in 1965 at age 30 and flying since then as a flight engineer, co-pilot, and pilot. In 1971, at age 37, the patient first noticed that his vision became fuzzy owing to glare when light was shining directly into his eyes. However, it was not until late in 1972 that he was found to have an early stage of cataracts, but, as he was still able to see 20/20 with each eye under the contrived dark-room conditions of the visual acuity test, he was approved for flying. He also passed this examination in May 1973. He was not disqualified from flying until September 1973, when he failed the examination because vision then was reduced to 20/40 in his right eye; nevertheless, his left eye was still capable of 20/20 despite the stage of cataractous change clearly evident in Fig. 1. This remarkable photograph, taken with a Kowa retinal camera used as an ophthalmoscope at a distance of 0·5 m and focused on the posterior surface of the crystalline lens, shows many minute areas of opacification of the posterior capsule. Although the patient's visual acuity was normal under the contrived illumination conditions for ordinary visual testing, severe obscuration of vision owing to glare occurred whenever the eye was illuminated from directly in front.

Pathology

The left lens of case 2 became available for histological study after cataract extraction in May

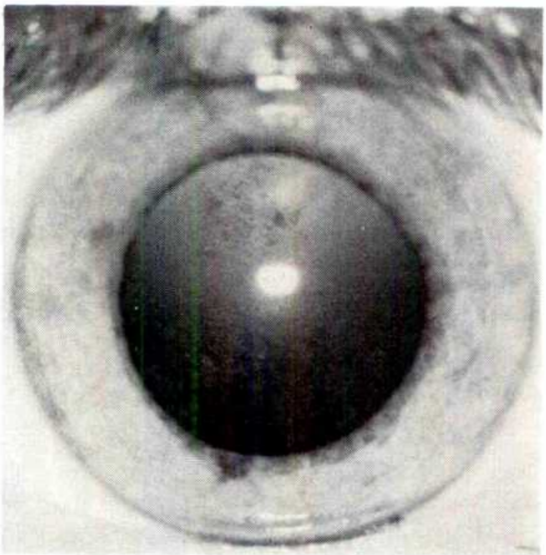

Fig. 1 *Photograph of left eye of airline pilot (case 9), with sharp focus on posterior surface of crystalline lens, where extensive capsular opacification is readily observed. Although visual acuity was recorded at 20/20 under contrived illumination conditions for usual testing, severe obscuration of vision due to glare occurred whenever the eye was illuminated from directly in front*

1976. Fig. 2 shows the anterior surface of the lens lying behind the iris. Note vacuolation and degeneration of the subcapsular epithelium, including pyknotic nuclei and irregular intercellular spacing. At the external surface of the anterior capsule there is a small remnant of iridial tissue, representing a proteopexic adhesion similar to that described in cataract after exposure to nonionising radiant energy (Zaret *et al.*, 1976).

Fig. 3 is a section at the posterior surface of the same lens. Note the capsule, where there are several discrete vacuolated areas of degenerated lens fibres abnormally adherent to its internal surface. These loci are separated by clear areas where the internal edge of the capsule is free of abnormal adhesions. These histological findings appear to provide an explanation for the honeycomb appearance of the posterior capsule as observed clinically by slit-lamp biomicroscopy.

Discussion

Many features about this cluster of cataract cases should be of concern to all physicians, not only those with special training in ophthalmology, epidemiology, and preventive, aerospace, and occupational medicine, but also others who use hertzian radiation as diathermy in either consulting room or operating theatre. However, before looking in that direction, the corollary of air safety should be considered.

Simply stated, the techniques of eye examination at present in use to certify operational aviation personnel are inadequate. They fail to identify the early stages of either capsular cataract or visual impairment. Better methods, including some simple new procedures such as testing for entopic glare function and detailed inspection of the lens capsule, should be incorporated immediately into the routine physical examination. Furthermore, in addition to lens opacification, macular and paramacular retinal lesions resembling the residua of subclinical inflammatory reactions have been reported in microwave workers (Aurell and Tengroth, 1973). Case 8 may represent an example of this type of retinal pathology at an early subclinical stage where the visual disturbances are still transient and, therefore,

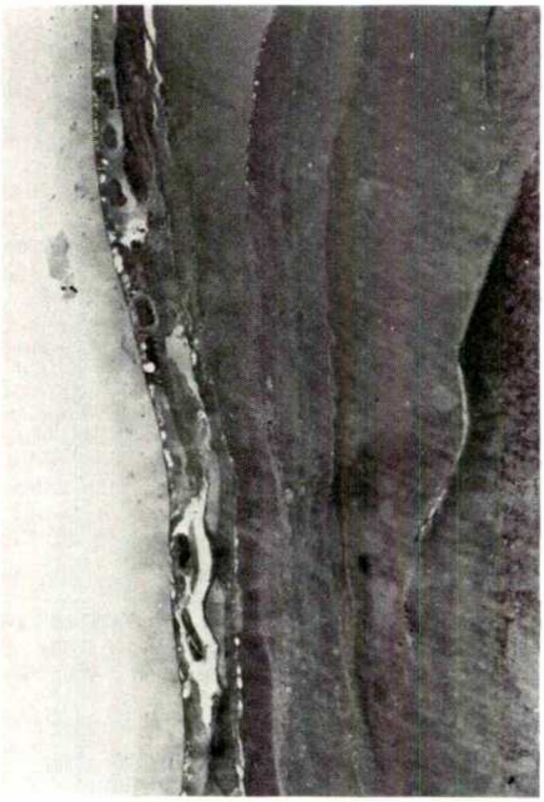

Fig. 2 *A microphotograph (× 440) of the anterior surface of the left lens of EC 121 aircraft radarman (case 2). Note aberrations in lens epithelial cells and remnant of posterior synechia indicating firm proteopexic adherence of iris to anterior lens capsule*

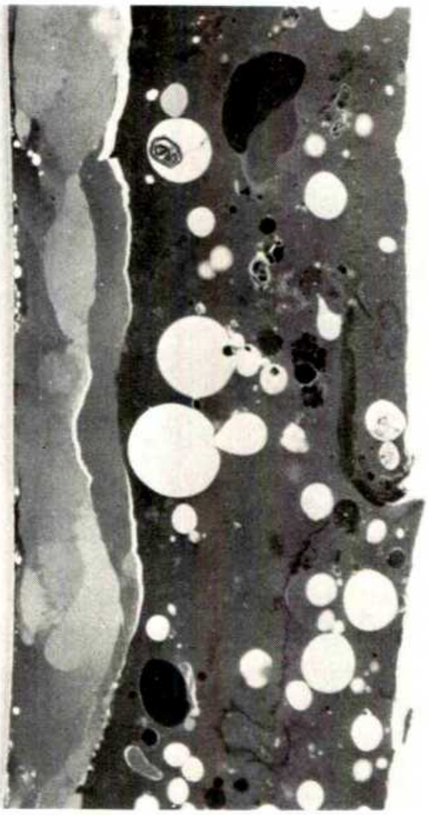

Fig. 3 *A microphotograph* (× 440) *of the posterior surface of the same lens (case 2). Note particularly the highly refractile internal edge of the capsule as the site where scattered areas of degenerated lens fibres are seen to be adherent. This correlates with the slit-lamp sign of honeycomb capsulopathy, the earliest clinically recognisable stage of hertzian radiation cataractogenesis*

subside by the time the ophthalmic examination is performed.

A few words about acquired capsular cataract may help us to understand some aspects of injury from nonionising radiation. During the nineteenth century capsular cataract was found to occur primarily among workmen in occupations with chronic or repeated environmental exposure to the radiant energy emitted from molten masses of glass or metal. It practically disappeared as a clinical entity during the first half of the twentieth century after it was established as a compensatable occupational disease (Legge, 1907), and employers instituted protective measures—goggles which reduce the transmission of infrared radiant energy.

Capsular cataract was known originally as one form of 'heat cataract' because most earlier investigators accepted the assumption it was caused by raised intraocular temperature: they did not recognise there could exist a nonthermal radiant energy effect *per se* at infrared band frequencies. The same 'thermal' bias was accepted initially to explain microwave cataractogenesis. However, with the development of a classification of a microwave cataract into acute, subacute, and chronic types (Zaret in Czerski, 1974b) it became apparent that, although acute microwave cataract had a thermal component presenting as a burn of the lens substance, chronic microwave cataract did not. Chronic microwave cataract develops slowly over a period measured in years and follows repeated irradiation at nonthermal intensities; it presents clinically as a gradual degradation of the lens capsule, without any evidence of burn, and resembles a delayed, purely radiational effect. Recently experiments have confirmed that chronic or repeated exposure to hertzian radiation at low field intensities produces changes principally in the lens fibres proximal to the posterior capsule (Williams *et al.*, 1975). Moreover, low field intensity or nonthermal irradiations have been shown to affect adversely hertzian radiation workers (Sadcikova in Czerski, 1974) the immunological response (Stodolnik-Baranska in Czerski, 1974), chromosomes (Heller and Teixeira-Pinto, 1959), and even the molecular structure of DNA and RNA (Frazer, 1976).

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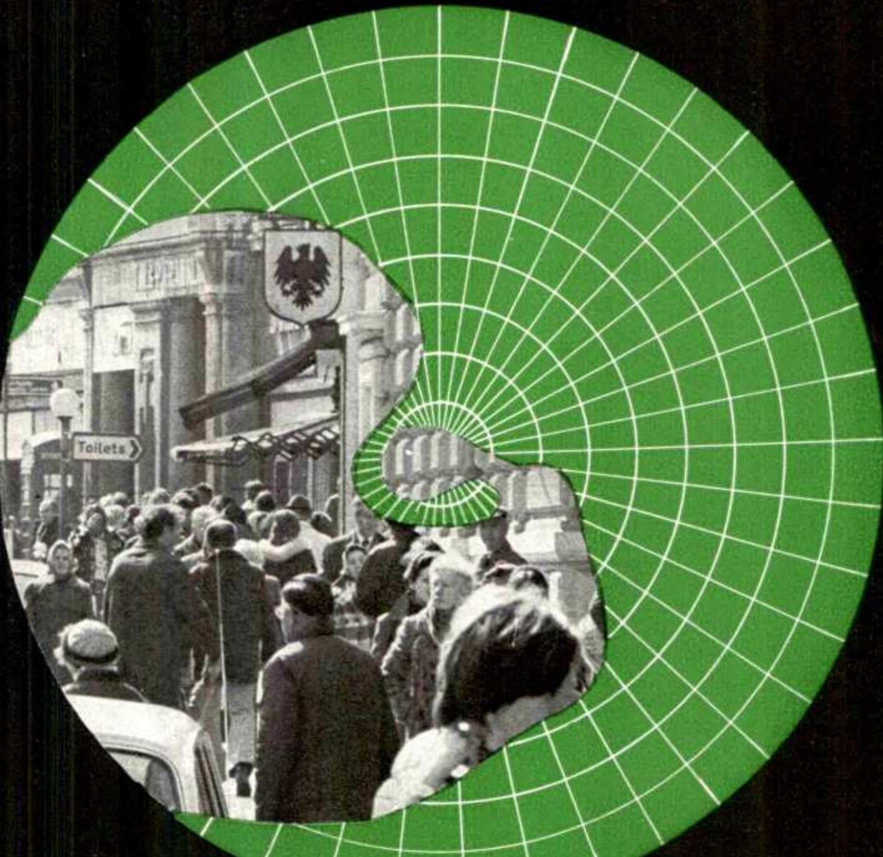

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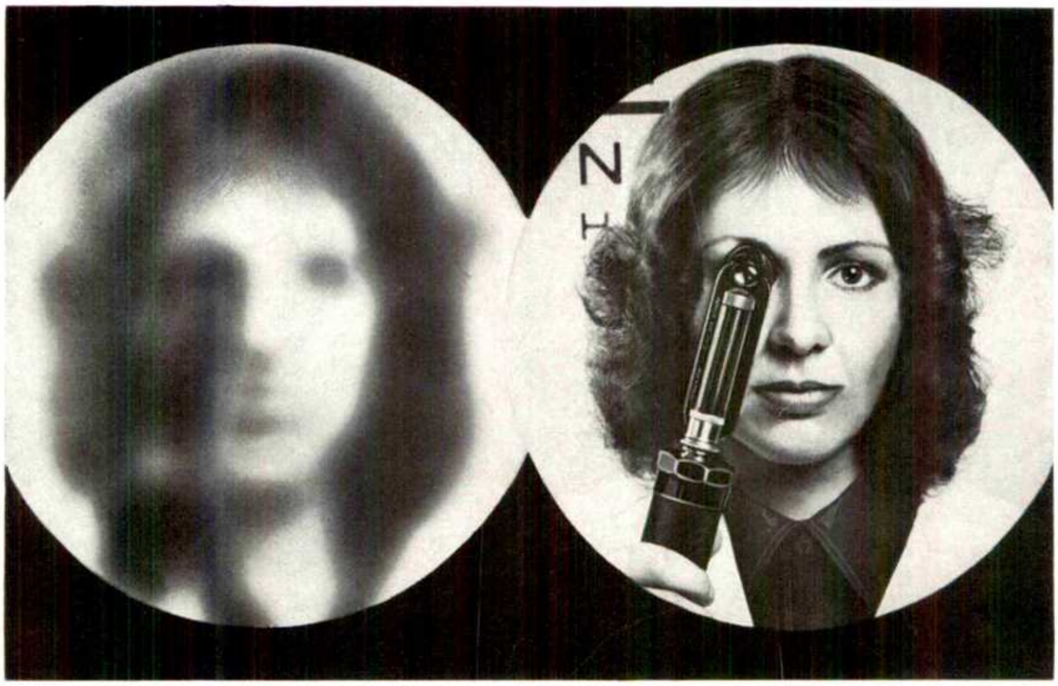

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Dilemma of the swollen optic disc: a fluorescein retinal angiography study

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SUMMARY In all of 100 consecutive patients referred for retinal angiography with a clinical diagnosis of probable or possible papilloedema a definite diagnosis was made from neurological assessment, neuroradiological investigations, and follow-up. The cases have been divided into 2 groups—those with proved papilloedema and those which have been called either normal or pseudopapilloedema. In all cases the retinal angiograms showed normal or increased optic disc vascularity and normal or increased early and late disc fluorescence. On the basis of these alone clear differences could be shown between the groups. All cases with papilloedema showed a combination of either excess late fluorescence with excess early fluorescence or excess late fluorescence with excess disc vascularity. Only 2 cases of pseudopapilloedema (both with optic disc drusen) showed this combination, and in both the pattern of disc fluorescence was different from that seen in papilloedema. Retinal angiography therefore seems to be of considerable value in differentiating true from pseudopapilloedema, though this is possible only when each stage of the angiogram is carefully studied.

The difficulties in differentiating pseudopapilloedema from true papilloedema are well known to ophthalmologists and neurologists. They become more difficult when symptoms of intracranial disease are vague and a decision to undertake potentially dangerous neuroradiological investigations is entirely dependent upon a correct interpretation of the disc changes (Hoyt and Pont, 1962). While papilloedema may often be diagnosed by conventional ophthalmoscopy in certain cases there may be doubt about the interpretation of the changes in the optic disc. In such instances diagnosis may be facilitated by retinal angiography (Barrios, 1963; David *et al.*, 1963; Miller *et al.*, 1965; Blair and Walsh, 1969; Bynke and Aberg, 1970).

After intravenous injection of sodium fluorescein retinal angiograms are said to differentiate papilloedema from pseudopapilloedema both in the early and later stages after injection (Miller *et al.*, 1965). Depending on the degree of disc swelling, angiograms done early after injection in patients with papilloedema show capillary dilatation, dye leakage, and microaneurysm formation. These changes are said to be absent in patients with pseudopapilloedema. In the later stages after injection there is leakage of dye beyond the margins of the disc (Barrios, 1963; Blair and Walsh, 1969). A third feature, a tendency of the veins to retain fluorescence, is said to occur in papilloedema (David *et al.*, 1963) and not in normal cases.

Initial optimism about the usefulness of this technique in differentiating true papilloedema from pseudopapilloedema, however, has not been entirely justified. Late fluorescence spreading beyond the margins of the disc is absent from some cases of papilloedema (Bynke and Aberg, 1970) and Sanders's classification of 5 types of papilloedema based on retinal angiograms emphasises some of the difficulties (Sanders, 1969).

Our own experience convinced us that a controlled study of this problem was needed. We have therefore reviewed the last 100 consecutive cases referred to us with a diagnosis of probable or possible papilloedema.

Patients and methods

The patients were referred for retinal angiography from a wide area around Newcastle. Most were from physicians within the Royal Victoria Infirmary, from the neurosurgeons and neurologists at the Regional Neurological Centre, or from the neurological and ophthalmological units at the Royal Victoria Infirmary. None were referred directly

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from general practitioners. All the patients referred by the various consultants were thought from the appearance of the optic disc to have either probable or possible papilloedema. Many had symptoms such as headache, dizziness, or visual failure which were thought possibly to indicate intracranial disease.

Colour photographs were taken of both discs, using a Zeiss Contax camera body loaded with Kodachrome II film (ASA 125, DIN 22), after pupillary dilatation with a combination of 1% cyclopentolate hydrochloride (Midrilate) and 10% phenylephrine hydrochloride.

For fluorescein angiography the fundus camera was connected to a Zeiss-Siemens flash generator and a Robot Recorder camera. The setting was further modified (Rosen, 1967) by inserting a fluorescence excitation filter (Ilford Bright Spectrum Blue 622) over the No. 7 aperture of the illuminating diaphragm and a barrier filter (Kodak Wratten 15) placed in the masking cone in the camera body. The first photograph was taken as soon as the intravenous injection of 3 ml 25% sodium fluorescein was completed, and about 5 to 8 seconds later the immediate phases of fluorescein flow were captured at 1-second intervals up to a period of 20 to 25 seconds after the injection. Later photographs were taken from both discs at 1, 2, 5, 10, 20, and 30 minutes after injection.

Follow-up data were obtained in all 100 cases, and in all a final definitive diagnosis was reached without reference to the retinal angiograms. Patients were allocated into 2 groups—firstly, those with papilloedema and, secondly, those whom we have called normal or who had pseudopapilloedema.

Most patients were included in the papilloedema group on the basis of proved raised intracranial pressure. They either had a tumour, found at operation, or had been diagnosed as suffering from benign intracranial hypertension, shown in most cases by ventriculography. A number of other patients in whom a local cause for the papilloedema was thought likely were included in this group. Most of them presented with visual failure (often unilateral) and were referred primarily because of doubts about the diagnosis. While many would question the use of the term papilloedema in this context, all these cases clearly had optic disc oedema for which a local cause was thought responsible.

In all the patients in the normal or pseudopapilloedema group either neurological investigations were negative or there was no change in the optic disc appearance during prolonged follow-up. Many had normal ventriculograms or airencephalograms and most of the others had a normal CSF pressure measured at lumbar puncture. The remainder have been seen at repeated follow-up visits for as long as 3 years, and in all the fundal appearances have remained unchanged. In none of these cases has there been evidence of either raised intracranial pressure or a local cause for the disc appearance.

Black-and-white prints (6 × 6 cm) were produced in all 100 cases showing the various stages after injection, as outlined above. These were examined by each of us without knowledge of the patients' diagnosis and the appearances noted. Optic disc vascularity was assessed as either normal or excessive from the appearances of the films taken within the first 20 seconds after injection. Early fluorescence was assessed as either normal or excessive on the films taken within 2 minutes of injection, and late fluorescence was assessed as either normal or excessive on the films taken 5 minutes and more after injection. These assessments were largely subjective, though based on our experience of the normal gained in the past 3 years.

Results

Forty-eight cases were diagnosed as papilloedema and the remaining 52 were classed as pseudopapilloedema or normal. In 30 patients raised intracranial pressure was the cause of the papilloedema. Table 1 shows their final diagnosis. The papilloedema in the other 18 cases was due to a local cause. Table 2 shows the final diagnosis reached in each case. The 2 undiagnosed cases both had unilateral visual impairment with the appearance of a swollen optic disc. In both the carotid angiogram and airencephalogram were normal and vision improved in both as the optic disc oedema decreased during follow-up. Neither case was thought by the clinician in charge or an ophthalmologist to be examples of papillitis. They may have been examples of retinal vasculitis (Hayreh, 1972).

Although clinically it was usually possible to separate patients with raised intracranial pressure from those with a local cause for the papilloedema this was rarely possible from the optic disc appearances alone, and the retinal angiogram appearances

Table 1 *Final diagnosis in 30 patients with papilloedema due to intracranial pressure*

Diagnosis	
Cerebral tumour	18
Benign intracranial hypertension	8
Subdural haematoma	3
Leukaemic meningitis	1
Total	30

Table 2 *Final diagnosis in 18 patients with papilloedema due to a local cause*

Diagnosis	
Papillitis	6
Hypertensive retinopathy	5
Ischaemic papillitis	3
Retinal vasculitis	1
Juxta papillary choroiditis	1
Undiagnosed	2
Total	18

in these patients in respect of the 3 features that we have considered—optic disc vascularity and early and late disc fluorescence—were indistinguishable. For the purpose of this analysis we have considered the 2 groups of papilloedema together.

The final diagnosis in many cases in the pseudopapilloedema group was not clear, though in all we were confident that we had excluded either intracranial disease or a local progressive lesion as a cause of the disc appearance. Most cases fell into the category of the 'structurally full disc' and the remainder we shall consider in the Discussion.

Table 3 shows an analysis of the 3 features of the retinal angiograms that we have discussed above, comparing their incidence in the 2 groups of cases. Excess disc vascularity, though more common in patients with papilloedema, was nevertheless present in 25% of those who were subsequently shown to have pseudopapilloedema or normal discs. All but 5 cases of papilloedema showed excess disc vascularity and all 5 were examples of mild or early papilloedema. Early disc fluorescence was thought to be excessive in 63% of the papilloedema cases but in only 2 in the pseudopapilloedema group. Late excess disc fluorescence was present in all cases of papilloedema but in only 4 cases (8%) of pseudopapilloedema.

Table 3 *Comparison of retinal angiogram appearances in patients with and without papilloedema*

	Retinal angiogram appearance		
Clinical group	*Excess disc vascularity*	*Excess disc fluorescence*	
		Early	*Late*
Papilloedema (n = 48)	43 (87%)	30 (63%)	48 (100%)
Pseudopapilloedema or normal (n = 52)	13 (25%)	12 (4%)	4 (8%)

Discussion

The aim of this study was to try to define the usefulness of retinal angiography in differentiating true from pseudopapilloedema. In all of the 100 cases a final diagnosis was made independently of the retinal angiographic changes, and hence it was possible to analyse the retinal angiograms blind in an attempt objectively to spot differences between the 2 groups of cases. A high percentage of cases of papilloedema showed excess disc vascularity and excessive early and late disc fluorescence. All showed late disc fluorescence and only 5 did not show excess disc vascularity. All these late cases, however, showed early and late excess fluorescence of the disc. In other words all cases of papilloedema showed either a combination of excess disc vascularity and excess late fluorescence or a combination of early and late excess disc fluorescence (Table 3).

The retinal angiogram in papilloedema is best considered in relationship to the pathology of papilloedema. From whatever cause, papilloedema is a result of capillary dilatation on the optic disc with transudation of fluid into the prelaminar portion (Schutta and Hedges, 1971). The retinal angiogram demonstrates not only the excess vascularity but, since the fluorescein dye leaks from the normal vessels in a similar fashion to the oedema fluid, staining of the optic disc by the dye measures the amount of transudate. The characteristic angiographic changes of papilloedema seen in our cases can thus be explained (Barrios, 1963; David *et al.*, 1963; Miller *et al.*, 1965; Shikano and Shimizu, 1968; Blaire and Walsh, 1969; Rosen, 1969; Bynke and Aberg, 1970).

The proportion of cases with papilloedema which show such changes will depend not only on the quality of film but also on the severity of the papilloedema and rapidity of its onset. This is covered fully by Sanders (1969). In very early papilloedema (a stage before Sanders's early group) we might expect oedema (measured by excess disc fluorescence) to be present without excess vascularity. Two of our cases of papilloedema showed this. The other 3 cases of papilloedema with disc fluorescence but no increase in disc vascularity were mild cases in which the early films were of poor quality. Disc fluorescence is, as we have stated, probably our best objective measure of continued oedema fluid leakage into the disc, and was seen in all our cases of papilloedema except the very chronic ones—Sanders's vintage group (Sanders, 1969). Certainly all our cases of papilloedema showed excess late disc fluorescence, though only two-thirds showed early leakage. Early leakage, however, seems to be more a function of rapidity of development than of severity of papilloedema. Those of our cases without early excess disc fluorescence were examples of chronic papilloedema. In summary, therefore, retinal angiography is a sensitive and accurate method of detecting papilloedema.

Of those patients in our normal or pseudopapilloedema group 25% showed excess disc vascularity. In isolation, therefore, this sign seems to be of little value and emphasises the wide normal variation in optic disc vascularity. Excess disc fluorescence, however, was seen in only 5 cases and only 1 of these had both early and late disc fluorescence (Table 4). Case 25 showed excess vascularity and early and late fluorescence, case 65 excess vascularity and early fluorescence, cases 2 and 41 late fluorescence only, and case 69 excess vascularity and late fluorescence.

As already stated, all our cases of papilloedema showed either excess vascularity and late fluorescence or early fluorescence and late fluorescence. Cases 65, 2, and 4 can be differentiated from true papilloedema on this basis alone and they will not be considered further. Cases 26 and 69, however, cannot be differentiated from papilloedema on the basis of pointers we have considered so far.

Case 26 was a 26-year-old woman who presented with headaches and was found to have abnormal fundi but no other abnormal neurological findings. Subsequent neurological investigation showed no abnormality. CSF pressure at lumbar puncture was normal. No change in the fundal appearance was seen during follow-up, though the patient's headaches improved. Clinically there was nothing to suggest that this patient had raised intracranial pressure or a local cause producing papilloedema, though retinal angiography showed excess vascularity and early and late fluorescence. Careful study of the angiograms, however, showed changes that were very different from those in a case of papilloedema (Fig. 1). In papilloedema of this degree the early leakage occurs in a very specific manner with the dye appearing as minute spots (microaneurysms) on the disc surface coalescing and producing diffuse disc staining after 2 to 5 minutes. The early films of case 26 (Fig. 2) do not show any 'spotty leakage' and fluorescence of the disc occurred diffusely within 20 seconds of injection. This appearance is not seen in papilloedema so soon after injection. We believe that this case represents an example of buried drusen of the optic disc.

Table 4 *Excess disc vascularity and excess early and late disc fluorescence in 5 cases of pseudopapilloedema*

Case No.	*Excess disc vascularity*	*Excess fluorescence*	
		Early	*Late*
26	Present	Present	Present
65	Present	Present	Absent
2	Absent	Absent	Present
4	Absent	Absent	Present
69	Present	Absent	Present

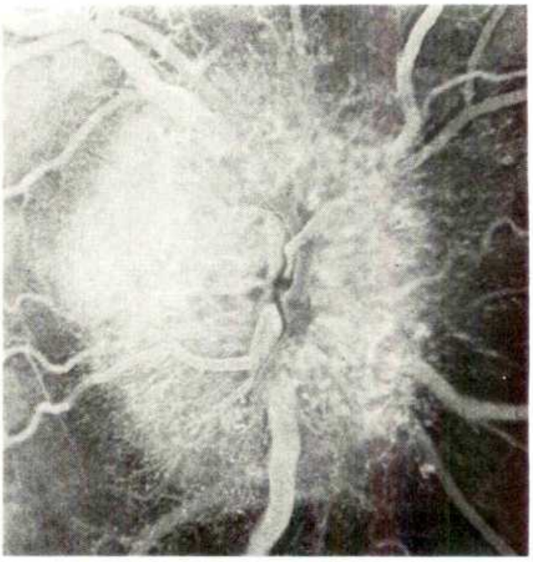

Fig. 1 *Retinal angiogram taken 15 seconds after injection of fluorescein in patient with papilloedema due to benign intracranial hypertension (case 78)*

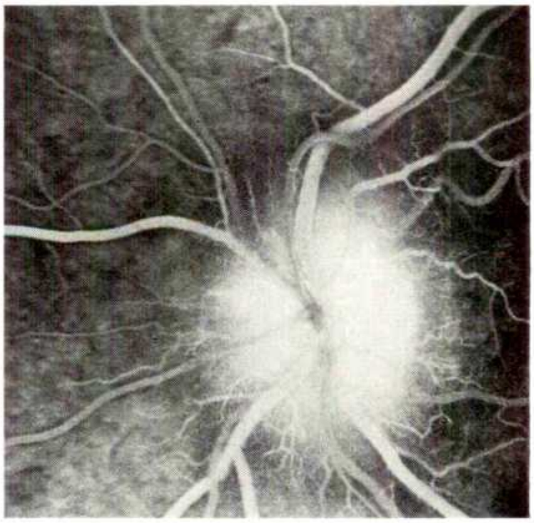

Fig. 2 *Retinal angiogram taken 15 seconds after injection of fluorescein in case 26*

Case 69 was a 32-year-old man who presented with headaches. Investigation elsewhere had shown normal carotid angiogram and normal CSF pressure at lumbar puncture. Two years after the initial presentation the fundal appearance was unchanged and the headaches had gone. The retinal angiogram in this case showed excess vascularity of the disc but no early disc fluorescence (Fig. 3). The later stages, however, showed disc fluorescence spreading beyond the disc margin. The important diagnostic feature is seen in the early film (Fig. 3) where, at position *B* the dye can be seen to be taken up in a local area. This focal early fluorescence is characteristic of giant drusen of the optic disc and vascularity of the disc is increased in these cases (Rosen 1969).

Our study shows that the retinal angiography is useful in differentiating true from pseudopapilloedema, though on the basis of excess disc vascularity and excessive disc fluorescence it is not diagnostic. The combination of late disc fluorescence with either early fluorescence or excessive disc vascularity probably indicates papilloedema, but in view of the 2 exceptions among our cases we would emphasise the importance of meticulous attention to detail when examining retinal angiograms.

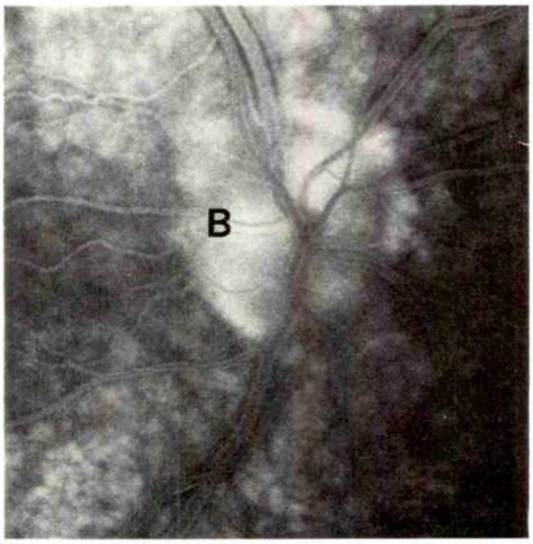

Fig. 3 *Retinal angiogram taken 1 minute after injection of fluorescein in case 69. Note dye taken up in local area* (B)

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British Journal of Ophthalmology, 1977, **61**, 390–393

Neoplasm of mixed mesenchymal and neuroepithelial origin of the optic nerve

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SUMMARY A case is reported of a 19-year-old male having right proptosis for 4 years because of a mixed meningioma and astrocytoma of the ipsilateral optic nerve. The sheath of this nerve is analogous to the leptomeninges, and neuroglial cells constitute the stroma of the nerve. Both meningioma and astrocytoma therefore can arise primarily in the optic nerve, and they may be combined in the same mass, forming a neoplasm of mixed mesenchymal and neuroepithelial origin.

Several instances have been recorded of neoplasm of mixed mesenchymal and neuroepithelial origin of the neuraxis but none involved the optic nerve (Shuangshoti and Panyathanya, 1974). Subsequently a unique case was encountered of an optic tumour of mixed mesenchymal and neuroepithelial type consisting of combined meningioma and astrocytoma. The tumour arising in the same optic nerve and producing progressive unilateral proptosis is now described.

Case report

A Thai male aged 18 years first noticed progressive exophthalmos associated with blurred vision of the right eye for 4 years before admission to hospital. Two years later the same eye was painful intermittently. One year before admission this eye was blind, but the ocular pain disappeared spontaneously. At the time of admission to hospital the patient complained of frontal headache.

EXAMINATION

The body temperature was 36·6°C, pulse 72, respirations 20, and blood pressure 120/80 mmHg. The right eye showed proptosis, conjunctival congestion, and central corneal opacity. The right pupil, 6 mm in diameter, was not reactive to light; the left pupil, 5 mm across, reacted well. The visual acuity of the left eye was 6/9, but there was no light perception in the right. In the right eye the retina was atrophic and the optic disc pale, but the left eye was normal.

Routine studies of the blood and urine yielded normal findings. *X*-rays of the orbits showed on the right side an enlarged optic foramen and thinning of the orbital walls in comparison to the left (Fig. 1). A right carotid angiogram revealed stretching of the intracranial portion of the internal carotid artery. The clinical impression was a retrobulbar tumour with intracranial extension.

OPERATION

The roof of right orbit was excised by an ipsilateral frontal craniotomy one day after the patient was admitted to hospital. A circumscribed retrobulbar mass, 2 cm in greatest dimension, arising in the right optic nerve and extending intracranially through the right optic foramen was almost totally removed. The left optic nerve was thin.

COURSE

Postoperatively the patient gained consciousness spontaneously. Nevertheless the left eye became blind, and diabetes inspidus occurred. A large volume of urine of low specific gravity (1·000 to 1·010) was recorded—as much as 6000 ml on some days. However, the diuresis was controlled by the administration of pitressin. The patient was eventually discharged four months after admission and did not return to the hospital.

PATHOLOGY

The specimen (Siriraj Hosp. S-17-5145) was fixed in 10% formalin and embedded in paraffin. The sections were stained with haematoxylin and eosin. Wilder's stains for reticulin fibres and Mallory's phosphotungstic acid haematoxylin (PTAH) stains for neuroglial fibres were also used.

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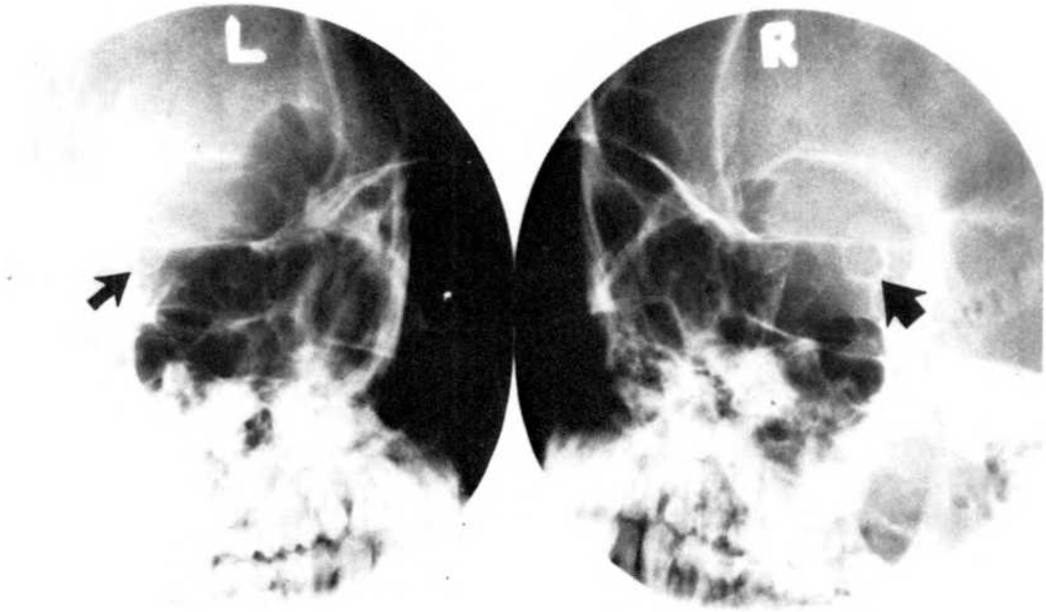

Fig. 1 *Orbital* x-*ray showing greater size of the right optic foramen* (arrow, right) *than of the left* (arrow, left). *Thinning is also noted of the orbital wall on the right side*

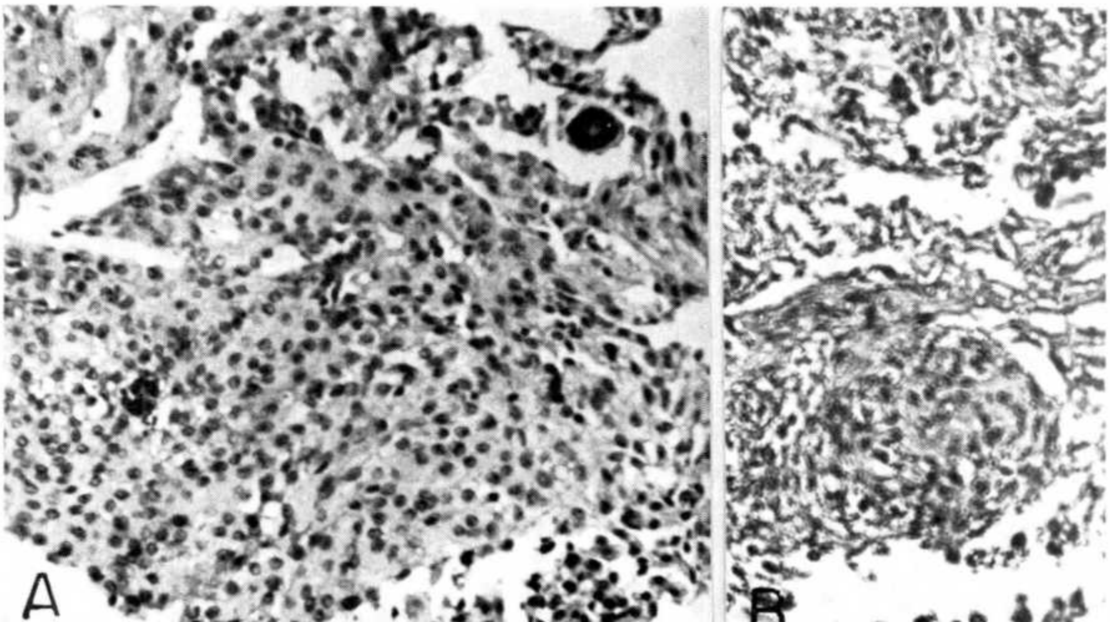

Fig. 2 *Portion of meningioma in the combined tumour from the right optic nerve showing:* A. *Sheet of meningocytes, two psammoma bodies at the right upper corner, and a calcific focus toward the left margin of the photomicrograph. Note syncytial appearance and occasionally vacuolated nuclei of meningocytes (H and E. ×100);* B. *Whorl of meningocytes, a diagnostic hallmark of the meningioma (H and E. ×100)*

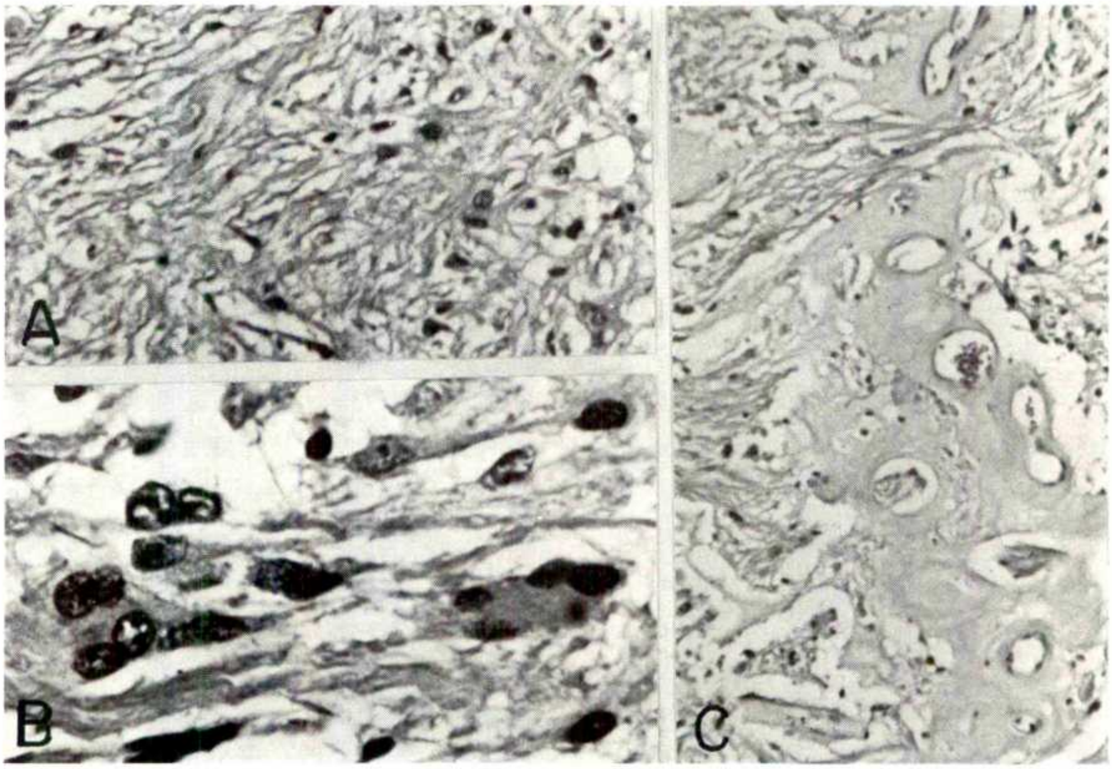

Fig. 3 *Portion of astrocytoma in the mixed tumour from the right optic nerve illustrating:* A. *Neoplastic astrocytes with numerous processes* (*H and E.* × 100). B. *More detail of neoplastic astrocytes. Note angular or elongated outlines with coarse processes, glassy cytoplasm, and vesicular and ovoid nuclei. Some astrocytes are multinucleated* (*H and E.* × 400). C. *Stromal blood vessels with considerably thick and hyalinised walls* (*H and E.* × 100)

Microscopically there were two different types of neoplastic cells forming the mass. One type was meningocytic (Fig. 2). The cells were plump and syncytial in appearance. The ovoid and vesicular nuclei were occasionally vacuolated. These meningocytes were arranged mainly in sheets and whorls within the space between the sheath of the optic nerve and the dura mater, with minimal infiltration into these two membranes. However, they did not extend beyond the dura mater or into the underlying optic nerve. A few psammoma bodies were scattered in this part of the neoplasm. Many coarse collagen fibres, a few reticulin fibres, and a moderate number of small thin-walled blood vessels composed the stroma of the tumour.

The other type of tumour cells was astrocytic (Fig. 3). They were disseminated within the optic nerve and characterised by their frequently angular outlines, with processes extending from corners and glassy cytoplasm. Some cells were elongated with polar processes. These processes were blue in PTAH preparations and were occasionally attached to the vascular adventitia. The vesicular nuclei were often eccentrically placed. The stromal blood vessels in this part of the tumour frequently showed thick and hyalinised walls, a characteristic vascular feature in the astrocytoma involving the optic region. Reticulin fibres were absent except for a few round some blood vessels. Foamy and haemosiderin-laden phagocytes were scattered in the lesion.

COMMENT

The diagnosis was a neoplasm of mixed mesenchymal and neuroepithelial origin (combined meningioma and astrocytoma) of the right optic nerve. The terms 'mixed' or 'combined' imply mingling of multiple types of neoplastic cells of both mesenchymal and neuroepithelial origin in the same mass or in juxtaposition.

Discussion

The development of the visual apparatus has been reviewed (Shuangshoti, 1973a). The sheath of the optic nerve is analogous to the leptomeninges; it contains meningocytes (arachnoidal cells), the mesenchymal derivatives. A meningioma can thus arise primarily in the optic sheath (Shuangshoti, 1973a; Shuangshoti and Panyathanya, 1973).

The retina is derived from the neuroepithelium originally lining the prosencephalon. The retinal ganglion cells yield nerve fibres which extend backwards into the optic stalk and become the optic nerve, chiasm, and tract (Shuangshoti, 1973a). The stroma of the retina and the optic nerve consists of glial cells of both neuroglial and microglial varieties, as in the central nervous system (Friedenwald *et al.*, 1952). The astrocytes and oligodendrocytes constitute the neuroglial interstitium of the retina and the optic nerve. Astrocytoma and oligodendroglioma therefore can arise in the retina as well as in the optic nerve (Jordano *et al.*, 1974). Some optic astrocytomas are associated with phacomatosis, as with tuberous sclerosis and neurofibromatosis (Shuangshoti and Panyathanya, 1972; Jordano *et al.*, 1974), but not in the present case.

In this case a unitary diagnosis cannot be made of either meningioma or astrocytoma because of the mingling of neoplastic meningocytes and astrocytes in the same mass. It is thus appropriate to call the lesion a neoplasm of mixed mesenchymal and neuroepithelial type. This category of mixed tumours comprises 1·6% of our previously reported series of 1028 intracranial neoplasms from Thailand (Shuangshoti and Panyathanya, 1974).

The components of neoplasm of mixed mesenchymal and neuroepithelial origin are diversified in accordance with the multipotential differentiation of mesenchyme or its derivatives (Willis, 1960) as well as commutation among different types of neoplastic neuroglia (Zimmerman, 1955; Shuangshoti and Netsky, 1971). The mesenchymal component in a mixed tumour thus may be a meningioma, rhabdomyosarcoma, neurilemmoma, lymphoma, plasmacytoma, and so on. The neuroepithelial part may be composed of various types of glioma or ganglioglioma. It is therefore not surprising to encounter mixed tumours of meningioma, lymphoma, and glioblastoma multiforme (Shuangshoti and Netsky, 1970); rhabdomyosarcoma, reticulum cell sarcoma, fibrosarcoma, and astrocytoma (Shuangshoti and Netsky, 1971); meningioma, ependymoma, and astrocytoma (Shuangshoti *et al.*, 1971; Shuangshoti, 1973b); lymphoma, plasmacytoma, astrocytoma, and ganglioneuroma (Shuangshoti and Samranvej, 1975); meningioma and oligodendroglioma (Tanaka *et al.*, 1975); and meningioma and astrocytoma as in the present tumour. The mode of occurrence of these neoplasms of combined mesenchymal and neuroepithelial origin has been discussed (Shuangshoti and Netsky, 1971).

The authors are grateful to Dr Chamriang Tantawatana, the attending ophthalmologist, and Professor Tinrat Stitnimankarn, head of the Department of Pathology, Siriraj Hospital, Mahidol University, for permission to study and report this case.

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British Journal of Ophthalmology, 1977, **61**, 394–398

Vasoformative properties of normal and hypoxic retinal tissue

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SUMMARY By cannulating the stroma of rabbit corneae, and introducing extracts of retina and vitreous from newborn kittens subjected to vaso-obliterative doses of oxygen, an attempt was made to test the hypothesis that ischaemic retinal tissue releases a factor with vasoformative properties. It was found that, although retino-vitreal extracts from the test animals elicited a positive response in just over half the experiments, the degree of corneal vascularisation provoked by extracts from intact control animals was only marginally less. Consequently our findings do not permit any definite answer regarding the existence of a specific factor responsible for the proliferation of new vessels on the retinal surface in states associated with retinal hypoxia.

Proliferation of blood vessels on the inner surface of the retina can complicate a number of conditions which have in common impaired perfusion of the underlying capillary circulation. Under such circumstances it has been suggested that the retinal tissue in a state of metabolic embarrassment liberates a factor with vasoformative properties able to diffuse into the vitreous and stimulate the growth of new capillaries on the front of the retina (Ashton *et al.*, 1954; Wise, 1956). As yet, however, direct evidence in support of this hypothesis has not been forthcoming.

In this report we describe an attempt to provide more positive evidence of a vasoformative factor in hypoxic retinal tissue using extracts of retinae from kittens which had been subjected to high concentrations of inspired oxygen. Vasoformative activity was sought by observing the effect of the extracts on the limbal blood vessels when introduced into the corneal stroma of healthy rabbits.

Materials and methods

INDUCTION OF RETINAL NEOVASCULARISATION

Five to 12 days after birth litters of kittens were maintained in a continuous atmosphere of 80% oxygen for 72 hours, by which time there was complete and irreversible obliteration of the retinal vasculature. The kittens were then transferred to normal air and 5 days later were given a lethal intraperitoneal dose of pentobarbitone. In all, 8 kittens were treated in this way. Since a period in air of about 10 days is required before new channels can be recognised on the retinal surface under these conditions (Ashton *et al.*, 1954) definitive neovascularisation was not seen at the time when the animals were killed.

PREPARATION OF RETINAL EXTRACTS

As soon as the kittens were deeply anaesthetised the eyes were enucleated and opened through the ora serrata to allow removal of the retinae. Pooled retinae were homogenised in 0·25 ml distilled water per retina in a motor-driven Teflon homogeniser at 1500 rpm for 1 minute with a pestle clearance of 0·15 mm. The homogenates were then centrifuged at 100 000 *g* for 1 hour at 4°C, and the supernates were collected and lyophilised. Extracts were prepared from 8 oxygen-treated and 5 normal control kittens of comparable age.

CORNEAL INTUBATION

Initially the extracts were dissolved in distilled water at a concentration equivalent to 1 retina or vitreous per 20 μl and drawn up into nylon tubes to give an equivalent of one extracted retina in each. The tubes were then sealed at one end, the other having been pulled out before filling to provide a very fine structure (0·6 mm external diameter) capable of being inserted between the lamellae of the corneal stroma of rabbit eyes. The catheters so formed were inserted into the corneae by a method similar to that introduced by Zauberman *et al.* (1969). This involved creating a track for subsequent passage of the catheter by introducing an iris repositor, moulded to the curvature of the cornea, through a small incision in the limbal sclera and advancing it to

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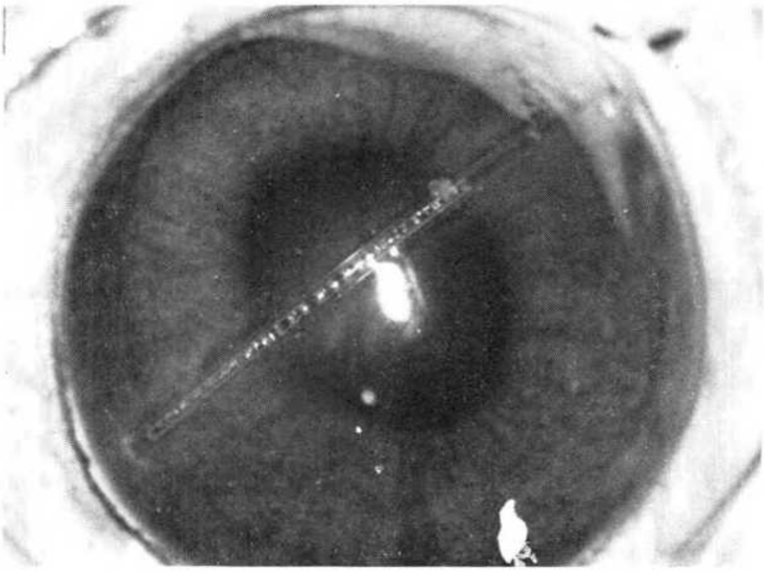

Fig. 1 *An enucleated eye showing a fine nylon catheter introduced between the stromal lamellae of the cornea via the perilimbal sclera to within 3 mm of the limbus on the opposite side.* × 7

within 2 to 3 mm of the opposite limbus (Fig. 1). The wider part of the tube, which acted as a reservoir for the extract, was passed round the circumcorneal region of the globe under the extraocular muscle insertions and held in place with silk sutures. Eleven tubes containing extracts from hyperoxygenated kittens and 6 tubes filled with extracts of normal retinae were inserted by this method. Ten identical operations using empty tubes were also performed.

In later experiments the extracts were mixed with a smaller (5 μl) amount of distilled water, and much shorter tubes were introduced directly through the central region of the corneal stroma to within 2 mm of the limbus. Seven tubes containing modified minimum Eagle's tissue culture medium were also inserted by this method.

Results

A positive response to the presence of the intracorneal catheter and its contents was marked by an

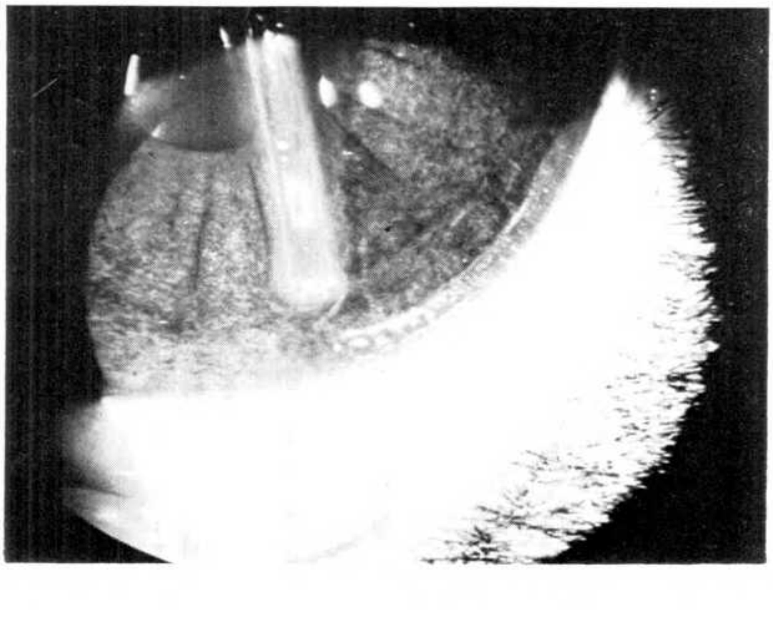

Fig. 2 *After insertion there has not been any vasoproliferative activity opposite the open end of an empty (short) tube. The whitish material in the lumen of the tube consisted mainly of macrophages and neutrophil polymorphonuclear leucocytes.* × 10

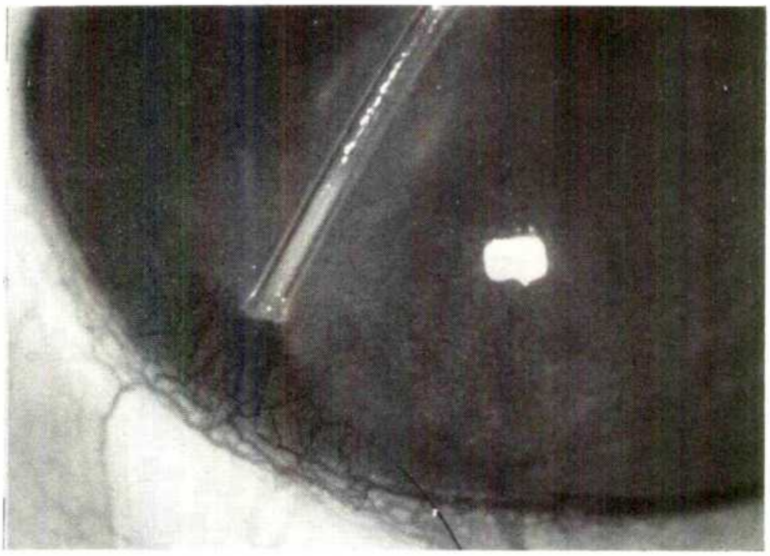

Fig. 3 *Intubation with retinal extract from a hyperoxygenated kitten is associated in this instance with vascular infiltration of the cornea as far as the orifice of the nylon tube.* ×10

initial engorgement and dilatation of the perilimbal vessels of the bulbar conjunctiva. This occurred within the first 2 to 3 days of the intubation and in some instances was the only response. In others the next few days saw a gradual proliferation of recognisable new vessels, which invaded the peripheral cornea opposite the open end of the tube to varying degrees (Figs. 2 and 3). In all animals assessment of the vascular response was made on the 10th day, after which the experiments were terminated, since pilot experiments had indicated that if vascularisation was going to occur it would be apparent by such a time. Clinically there was no sign of infection or ulceration in any of the intubated corneae.

Semiquantitative *in vivo* assessment of the vascular infiltration was attempted and the results are summarised in Table 1. Scoring on an arbitrary scale, we found that the mean vasoproliferative response to hyperoxygenated retinal extracts was 1·31 units; to extracts of normal control retinae the mean response was 1·11 units; whereas the mean response to the presence of an empty tube was 0·36 units. Experiments in which the tubes were filled

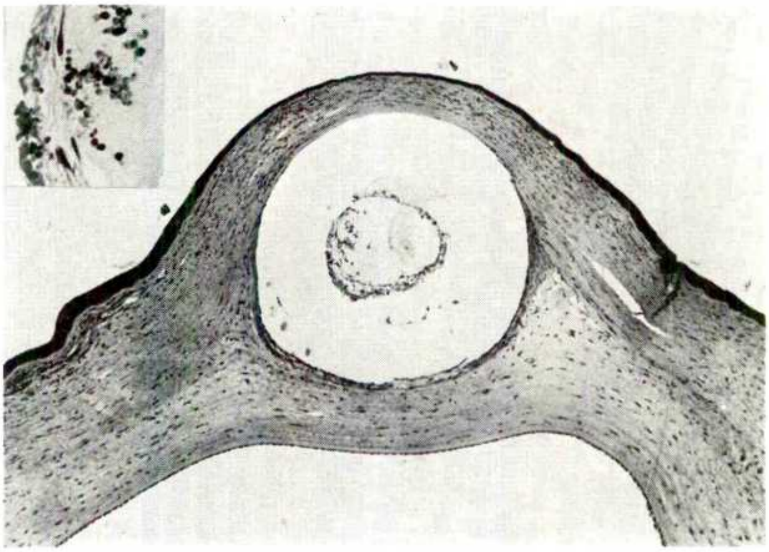

Fig. 4 *Section of cornea passing close to the open tip of the tube and showing its position in the mid-stroma.* Inset: *At higher magnification the cellular infiltrate at the tip of the tube is seen to comprise polymorphs, mononuclear cells, and fibroblasts. H and E.* ×65 (inset ×260)

Table 1 *Degree of corneal vascularisation stimulated by retinal extracts and tissue culture medium in individua. experiments*

Nature of stimulus	*Expt. no.*	*Extent of corneal vascularisation*		*Type of intracorneal tube*
Post-hyperoxygenation retinal extract	1	++++		Long
	2	++		,,
	3	++		,,
	4	+		,,
	5	+		,,
	6	+++		,,
	7	+++		,,
	8	–	Mean score 1·31	,,
	9	–		,,
	10	–		,,
	11	–		Short
	12	++		,,
	13	–		,,
	14	+++		,,
	15	–		,,
	16	–		,,
Normal retinal extract	1	–		Long
	2	++		,,
	3	++		,,
	4	+	Mean score 1·11	,,
	5	–		,,
	6	++++		,,
	7	–		,,
	8	+		Short
	9	–		,,
Empty tube	1	–		Long
	2	+		,,
	3	+		,,
	4	–		,,
	5	–		,,
	6	–		,,
	7	–	Mean score 0·36	,,
	8	–		,,
	9	–		,,
	10	–		,,
	11	–		Short
	12	–		,,
	13	+++		,,
	14	–		,,
Modified Eagle's tissue culture medium	1	++++		Short
	2	++++		,,
	3	–	Mean score 2·14	,,
	4	–		,,
	5	+++		,,
	6	+		,,
	7	+++		,,

Basis of scoring:
+ Slight engorgement of limbal vessels with minimal (<1 mm) invasion of cornea by 1 or 2 capillaries
++ More obvious limbal vessel engorgement with larger number of intracorneal capillaries
+++ Corneal vascularisation up to 2 mm
++++ Vessels impinging on open end of intracorneal tube

with tissue culture medium suitable for growing vascular endothelium *in vitro* gave a mean vasoproliferative response of 2·14 units.

Vascularisation of the cornea in areas other than opposite the open end of the tube, e.g., in the vicinity of the limbal incision through which the longer tubes were introduced, was discounted for the purposes of the study.

Histological examination of eyes with intracorneal vascular proliferation showed scanty leucocytes, mainly macrophages, but also including very occasional neutrophil polymorphonuclear cells, adjacent to the newly formed vessels. Macrophages were also seen around and within the tip of the implanted tube (Fig. 4), while in experiments in which a short tube was used a little downgrowth of surface epithelium was also seen. In no instance, however, was there any sign of infection or epithelial disturbance in relation to the tip of the tube.

Discussion

Although the purpose of this series of experiments was to test the hypothesis that hypoxic retinal tissue releases a factor with vasoformative properties, the results fail to provide an unequivocal answer. The response by conjunctival vessels at the corneal limbus to extracts of retina and vitreous from kittens recovering from the vaso-obliterative effects of excessive amounts of oxygen was hardly any better than that engendered by retinal extracts from normal control animals. This finding is open to one or more interpretations.

It is possible that both the normal and the hypoxic retinal extracts acted as non-specific tissue culture media by providing a source of essential metabolites. The experiments in which a modified Eagle's tissue culture medium was implanted in the cornea adequately demonstrated the capacity for this type of vascular growth to occur and showed that the presence of a peculiarly vasoformative factor is not obligatory. Consequently it is possible that the vasoformative potential of retinal tissue extracts is due to the presence of substances with similar nutritive properties. Their presence in healthy retina, albeit at a low concentration, may be necessary to preserve the existing physiological circulation, particularly as it has been found that the vascular proliferation stimulated by vasoformative factor obtained from malignant neoplasms regresses if the factor is withdrawn (Folkman, 1971). Consequently, the difference between normal and ischaemic retinae as regards their vasoformative potentials might be one of degree rather than of kind, the difference being insufficient to be readily detected in our essentially qualitative tests.

It may, however, be necessary to draw a distinction between growth permitted by the provision of a rich source of nutrients, as in tissue extracts, and specific mitogenesis by an agent which is not itself incorporated in the newly formed tissue. For, if the neovascularisation seen in the presence of retinal hypoxia is due to a simple tissue culture effect, it is difficult to account for the lack of similar proliferative activity on the part of the adjacent glial cells and the retinal pigment epithelium.

Again, how nutrients comparable to those represented in tissue culture media could be increased in hypoxia is uncertain for, although it has been considered for many years that the products of tissue autolysis, particularly those of nuclear origin (Fischer, 1939), can stimulate vascular proliferation in other organs (Cameron, 1952), retinal neovascularisation is not associated with overt necrosis. On the contrary, it is almost axiomatic that preretinal vessels develop in hypoxic as opposed to anoxic states, and it is difficult to believe that metabolically embarrassed but nevertheless viable retinal tissue would provide a better source of nutrients than would the products of infarction.

Recently Chen and Patz (1976) have shown that the vitreous of newborn puppies contains a soluble protein fraction which disappears over a period of about a month as vascularisation of the retina progresses to completion. Whether the presence of a similar protein in our own control kittens can be invoked to account for the proliferation of vessels at the corneal limbus will depend on whether this moiety is subsequently shown to be causally or only secondarily related to retinal angiogenesis.

Evidence has also been presented indicating the importance of neutrophil polymorphonuclear leucocytes in the pathogenesis of corneal vascularisation, whether as a direct or intermediate factor (Fromer and Klintworth, 1975a, 1975b, 1976), and although leucocytic infiltration of the cornea in the present experiments was not particularly impressive their participation in the vascular response stimulated by retinal tissue cannot be excluded.

It is clear that much work is still to be done if the release of a specific vasoformative factor by retinal tissue is to be demonstrated or refuted. Much of the problem lies in finding a wholly reliable method by which to test any postulated factor, wherein the difficulty in distinguising between peculiarly proliferative stimuli and the mere provision of metabolites essential for endothelial cell growth is excluded. A test in which local factors, such as may well be involved in using the cornea as a substrate (Ashton and Cook, 1953; Cogan, 1962; Fromer and Klintworth, 1975a), are absent is also desirable. There is also an obvious need to confirm and categorise the protein composition of the vitreous of newborn animals with incompletely vascularised retinae.

We are much indebted to Professor N. Ashton for advice and encouragement in the conduct of this work, to Miss E. Robins for technical assistance, and Mrs A. Wood for secretarial help.

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Treatment of early diabetic retinopathy with cyclandelate

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SUMMARY In order to assess the effect of cyclandelate on the abnormal permeability of the blood-retinal barrier which occurs in diabetic patients before any other lesions are apparent in the retina a well-controlled, double blind, and paired trial was carried out in 22 patients. The treatments were randomised. The permeability of the blood-retinal barrier was assessed by vitreous fluorophotometry. Each patient was examined before being involved in the trial and then another 3 times with 1 month's interval. The total duration of treatment was 3 months.

The results showed that the breakdown of the blood-retinal barrier as evidenced by the degree of abnormal fluorescein penetration into the vitreous suffered a significant decrease in the diabetic patients treated with cyclandelate when compared to the patients submitted to placebo administration, and this effect is particularly apparent in the third month of treatment.

It is now widely recognised that the major problem in diabetes mellitus does not arise acutely from lack of control of the carbohydrate metabolism, but from the insidiously developing vascular complications (Ditzel and Standl, 1975). The morbidity and incapacity associated with these complications are staggering, this being particularly true with diabetic retinopathy, which is nowadays one of the major causes of blindness.

In order to prevent this dramatic outcome it is necessary to detect the disease at a very early stage and to develop means of stopping its further progress. Its detection at a reversible stage and its immediate and effective treatment would be ideal.

It has recently been shown by our group that a significant disturbance of the blood-retinal barrier is present in diabetic patients with apparently normal fundi, this disturbance being apparently reversible (Cunha-Vaz *et al.*, 1975). This was made possible by the introduction of vitreous fluorophotometry, a new clinical quantitative method for the study of the blood-retinal barrier.

There is also some evidence that from the early onset of the disease diabetics may suffer from inumerable cellular hypoxic injuries, caused by the association of an increase in oxygen demand (Joslin, 1923; White, 1939) and a disordered oxygen delivery (Ditzel and Rooth, 1955; Ditzel and Standl, 1975b).

It is therefore reasonable to consider the possibility that the oxygen-dependent active transport mechanisms of the blood-retinal barrier are altered by these fluctuations in tissue oxygen tension and that any drug which has a protective action against hypoxia may influence favourably the course of the disease.

Cyclandelate was the drug chosen for this trial because it has been shown to have a protective action against brain hypoxia (Funcke *et al.*, 1974). In the past 10 years a number of papers have been published in which it was shown that cyclandelate treatment was followed by dilatation of cerebral vessels (Kuhn, 1966) and increased cerebral circulation (O'Brien and Veall, 1966). Improvement of mental functions in geriatric patients treated with the drug has been noted by Drift (1961), Ball and Taylor (1967), and others. These studies pointed, however, to an effect or effects of the drug on cerebral metabolism other than those indicated by a direct action on the tone of cerebral blood vessels. It has, indeed, been shown recently that cyclandelate enhances the resistance of rats and mice to hypoxia and attenuates or prevents the disturbances in the EEG of rats due to lack of oxygen (Funcke *et al.*, 1974). Cyclandelate has also been shown to increase the penetration of glucose

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into rat brain, and it is now accepted that the therapeutic efficacy of cyclandelate in cerebrovascular insufficiency may be based not merely on improved blood flow but also on stimulation of active glucose uptake by the brain.

The aim of this study is therefore to assess the effect of cyclandelate on the permeability of the blood-retinal barrier in diabetic patients, before there are any apparent retinal lesions, and when a complete recovery may be expected.

Method and evaluation

The trial was started as well-controlled, double blind, and paired and completed as such. The treatments were randomised. The parameter measured was the permeability of the blood-retinal barrier as evidenced by the penetration of fluorescein after intravenous injection.

The trial was carried out with adult diabetic patients which were being followed up as outpatients in the Diabetes Clinic of Coimbra University Hospital. There were 6 men and 16 women, ranging from 26 to 80 years of age, and averaging 52·4 years. Patients having a history of eye disease or showing any retinal lesions were excluded from this trial. Only patients with maximal visual acuity, normal ophthalmoscopic and slit-lamp pictures, and normal retinal fluorescein angiography were admitted to the population.

Patients were admitted to the trial in 12 pairs. One member of each pair was treated with cyclandelate and the other with placebo. A patient who dropped out during the course of the trial was replaced, as well as the other from that pair. One of these pairs dropped out, however, only in the last month of the trial and could not be replaced. By the end of the trial there were, therefore, 11 pairs.

The details of the trial were explained to each patient and consent was obtained. Each individual was assigned to either cyclandelate or placebo, as determined by a table of random numbers.

The doses of cyclandelate were standardised at 400 mg/capsule, 4 times daily. The total treatment duration was 3 months. The capsules of cyclandelate and placebo were provided by Mycopharma-Brocades. The key to the randomisation codes was kept by the local pharmacist and was unknown to the examiners until the trial was completed. No other preparation with vascular effects was used by the patients during the course of the trial.

Assessment of the permeability of the blood-retinal barrier

The permeability of the blood-retinal barrier was assessed by vitreous fluorophotometry (Cunha-Vaz *et al.*, 1975). The apparatus consisted essentially in a model 360 Haag-Streit slit-lamp which was modified by adapting a new source of illumination, appropriate filters, a photometric detection system, and a device for electrical registration of the movement of the instrument. Each patient was assessed 4 times, the first, before being involved in the trial, the second, at the end of the first month, the third at the end of the second month, and the fourth after the 3-month treatment. For these examinations a 10 ml intravenous injection of 10% sodium fluorescein was immediately followed by fluorescence angiography, performed with the Topcon TRC-F3 and by vitreous fluorophotometry 1 hour later. The fluorophotometric curves were recorded by a Polaroid camera. Because the values in the anterior vitreous, near the lens, are variable and influenced by fluorescein penetration through anterior routes, only the posterior half of the curve was analysed. The lower area A as indicated in Fig. 1 was roughly integrated, this value representing a true value of the concentration of fluorescein in the posterior vitreous.

The values obtained for these areas in each patient are presented in Table 1. These areas were named A_0, A_1, A_2, and A_3, according to the occasion of their recording, before the trial, after the first month, after the second month, or at the end of the third month, respectively.

The mean values of areas 0, 1, 2, and 3 in each group of patients were first compared in order to detect any general difference in behaviour between the 2 groups.

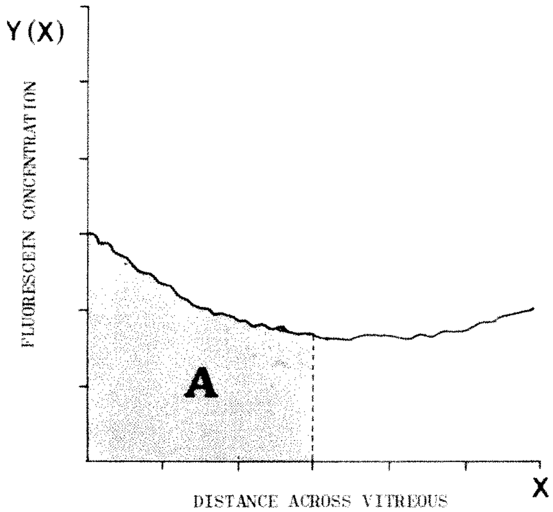

Fig. 1 *Typical fluorophotometric curve. The lower area, A under the curve represents a true value of the concentration of fluorescein in the posterior vitreous*

Table 1 *Values of fluorescein penetration into the posterior vitreous in the 4 examinations during the 3-month trial*

Placebo							*Cyclandelate*						
S. No.	*Age/Sex*	*Fluorescein penetration*				*Clinical information*	*S. No.*	*Age/Sex*	*Fluorescein penetration*				*Clinical information*
		A_0	A_1	A_2	A_3				A_0	A_1	A_2	A_3	
1	60/F	6·1	7·3	9·2	9·2		2	59/F	3·7	6·7	8·3	7·5	
4	50/F	5·4	4·1	6·9	7·0		3	80/F	9·3	9·4	11·9	10·2	
6	47/M	4·4	4·0	6·6	5·9		5	51/F	4·8	5·9	9·4	9·7	
8	42/F	3·3	6·7	5·7	8·4		7	55/M	4·6	6·3	9·1	9·1	Minimal hard exudates
9	33/F	6·7	6·5	6·6	6·9		10	26/F	5·4	7·9	4·7	4·8	
12	68/M	7·5	7·6	8·4	9·6		11	57/M	6·2	6·0	7·1	4·9	
15	64/F	5·9	5·9	9·2	10·3	Minimal hard exudates	16	42/F	7·8	6·0	7·0	5·4	
18	44/M	4·4	4·0	5·5	5·5		17	66/F	4·7	7·0	8·2	8·2	
20	46/F	3·6	6·8	10·2	9·1		19	60/F	4·6	6·1	7·6	6·5	
21	49/M	1·7	3·7	5·3	7·6	Hard exudates; signs of leakage on angiography	22	50/F	2·2	3·6	7·5	4·9	
26	42/F	4·8	4·0	8·7	10·0	Signs of leakage on angiography	25	61/F	6·0	6·4	7·7	6·7	
Mean		4·89	5·51	7·48	8·14				5·39	6·48	8·05	7·08	

The parameter that was used to test efficacy of the drug *v.* the placebo was the difference between the fluorescein concentrations in the posterior vitreous at the final examination, represented by A_3, and the fluorescein concentrations at the previous visits (A_2, A_1, and A_0).

For each patient (11 drug, 11 placebo) these differences ($A_3 - A_0$, $A_3 - A_1$, and $A_3 - A_2$) were subjected to statistical analysis. A final complementary analysis was made taking into account simultaneously for each patient, the differences $A_1 - A_0$ and $A_3 - A_2$, in order to highlight the corrective action of the drug on the abnormal permeability of the blood-retinal barrier. $A_1 - A_0$ represents the natural evolution of the disease, the effect of treatment being then minimal; $A_3 - A_2$ represents best the effect of treatment.

The following standard statistical methods were used: Student's *t* test and standard deviation.

CLINICAL ASSESSMENT

The visual acuity was tested for each patient and he was examined 4 times by ophthalmoscopy, during the course of the trial, at the beginning and at the end of each month.

Results

Assessment of the permeability of the blood-retinal barrier by vitreous fluorophotometry

The mean values of the areas under the fluorophotometric curves, representing the fluorescein penetration into the posterior half of the vitreous, obtained from each patient (11 placebo, 11 cyclandelate) and from the 4 examinations were graphically plotted (Fig. 2). The figure shows a well-defined pattern of progressive increase in the permeability of the blood-retinal barrier, well evidenced by the increased fluorescein penetration into the vitreous, in the placebo-treated patients, during the 3-month period of the trial. This pattern appeared, however, to be completely inverted during the third month of treatment in the patients receiving cyclandelate, suggesting a definite improvement in the conditions of abnormal permeability of the blood-retinal barrier which characterises the early stages of retinal involvement in diabetes.

Fig. 2 *Patterns of fluorescein penetration into the posterior vitreous, in placebo and cyclandelate treated patients, during the 3-month trial*

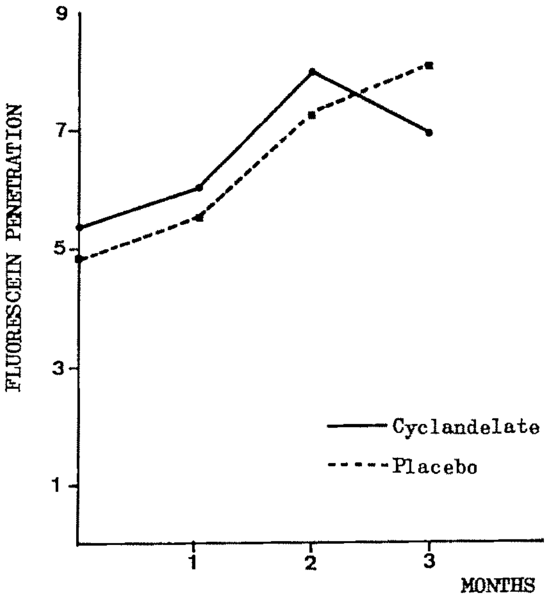

Table 2 *Differences in fluorescein penetration into the posterior vitreous between the last (A_3) and the initial examination (A_0)*

Placebo		*Cyclandelate*	
Series No.	$A_3 - A_0$	*Series No.*	$A_3 - A_0$
1	+3·1	2	+3·8
4	+1·6	3	+0·9
6	+1·5	5	+4·9
8	+5·1	7	−4·5
9	+0·2	10	−0·6
12	+2·1	11	−1·3
15	+4·4	16	−2·4
18	+1·1	17	+3·5
20	+5·5	19	+1·9
21	+5·9	22	+2·7
26	+5·2	25	+0·7
Mean	+3·2		+1·6
±SD	±0·616		±0·736

$t = 1{\cdot}74$; DF = 20; $0{\cdot}1 < P > 0{\cdot}05$.

This finding is substantiated when the differences in fluorescein concentration in the posterior vitreous between the last and the previous visits were analysed and the values obtained from patients given placebo capsules compared with the values obtained from cyclandelate-treated patients. The differences in fluorescein penetration, i.e., breakdown of the blood-retinal barrier, between the last visit (A_3) and the initial examination (A_0) are significantly different at the 10% level between the 2 groups of patients, placebo and cyclandelate ($t = 1{\cdot}74$; DF = 20; $0{\cdot}1 < P > 0{\cdot}05$; Table 2).

This level of significance increases, however, when the differences in fluorescein penetration are taken between the last visit and the second and third examinations, after 1 and 2 months of treatment, respectively. The differences between the last visit and the second examination ($A_3 - A_1$), between the 2 groups of patients, are significant at the 2% level ($t = 2{\cdot}7$; DF = 20; $0{\cdot}02 < P > 0{\cdot}01$; Table 3). Finally, the differences between the final observation and the third examination ($A_3 - A_2$) show a highly significant difference between the 2 groups of patients ($t = 3{\cdot}6$; DF = 20; $0{\cdot}005 < P > 0{\cdot}001$; Table 4). These results show clearly that cyclandelate has a beneficial effect upon the breakdown of the blood-retinal barrier which is present in the early stages of diabetic retinopathy, preventing its progressive increase, well evidenced in patients receiving placebo capsules. The results indicate also that this beneficial effect is particularly marked after a period of treatment of 2 months. The fact that the full effect of cyclandelate is especially well evidenced in the third month of treatment, in contrast to the first month when its activity appears to be minimal, prompted us to compare the differences between the third month of treatment ($A_3 - A_2$) and the first month ($A_1 - A_0$), i.e. $(A_3 - A_2) - (A_1 - A_0)$ between the 2 groups. The statistical analysis of these differences shows a highly significant difference between the 2 groups ($t = 4{\cdot}4$; DF = 20; $P < 0{\cdot}001$; Table 5).

Table 3 *Differences in fluorescein penetration into the posterior vitreous between the end of the trial (A_3) and the end of the first month (A_1)*

Placebo		*Cyclandelate*	
Series No.	$A_3 - A_1$	*Series No.*	$A_3 - A_1$
1	+1·9	2	+0·8
4	+2·9	3	+0·8
6	+1·9	5	+3·8
8	+1·7	7	+2·8
9	+0·4	10	−3·1
12	+2·0	11	−1·1
15	+4·4	16	−0·6
18	+1·5	17	+1·2
20	+2·3	19	+0·4
21	+3·9	22	+1·3
26	+6·0	25	+0·3
Mean	+2·6		+0·6
±SD	±0·475		±0·534

$t = 2{\cdot}7$; DF = 20; $0{\cdot}02 < P > 0{\cdot}01$.

Table 4 *Differences in fluorescein penetration into the posterior vitreous between the end of the trial (A_3) and the end of the second month (A_2)*

Placebo		*Cyclandelate*	
Series No.	$A_3 - A_2$	*Series No.*	$A_3 - A_2$
1	0	2	−0·8
4	+0·1	3	−1·7
6	−0·7	5	+0·3
8	+2·7	7	0
9	+0·3	10	+0·1
12	+1·2	11	−2·2
15	+1·1	16	−1·6
18	0	17	0
20	−1·1	19	−1·1
21	+2·3	22	−2·6
26	+1·3	25	−1·0
Mean	+0·65		−0·96
±SD	±0·357		±0·298

$t = 3{\cdot}6$; DF = 20; $0{\cdot}005 < P > 0{\cdot}001$.

These results indicate clearly that the breakdown of the blood-retinal barrier as evidenced by the degree of abnormal fluorescein penetration into the vitreous suffered a significant decrease in the diabetic patients treated with cyclandelate when compared to the patients submitted to placebo administration, and that this effect is particularly apparent after 2 months of treatment.

CLINICAL ASSESSMENT

The other examinations performed agree, although in a less clear manner, with the fluorophotometric results. As regards the clinical picture, the cases under study are of such nature that only signs of worsening can be accepted as true changes. The visual acuity remained maximal in every patient

Table 5 *Differences in fluorescein penetration between the third month of the trial ($A_3 - A_2$) and the first month ($A_1 - A_0$)*

Placebo				*Cyclandelate*			
Series No.	$A_3 - A_2$	$A_1 - A_0$	*Difference*	*Series No.*	$A_3 - A_2$	$A_1 - A_0$	*Difference*
1	0	+1·2	−1·2	2	−0·8	+3·0	−3·8
4	+0·1	−1·3	+1·2	3	−1·7	+0·1	−1·8
6	−0·7	−0·4	−0·3	5	+0·3	+1·1	−0·8
8	+2·7	+3·4	−0·7	7	0	+1·7	−1·7
9	+0·3	−0·2	+0·5	10	+0·1	+2·5	−2·6
12	+0·6	+0·1	+0·5	11	−2·2	−0·2	−2·0
15	+1·1	0	+1·1	16	−1·6	−1·8	+0·2
18	0	−0·4	+0·4	17	0	+2·3	−2·3
20	+1·1	+3·2	−2·1	19	−1·1	+1·5	−2·6
21	+2·3	+2·0	+0·3	22	−2·6	+1·4	−4·0
26	+1·3	−0·8	+0·5	25	−1·0	+0·4	−1·4
Mean			+0·02				−2·07
SD			±0·302				±0·455

$t = 4{\cdot}4$; DF = 20; $P < 0{\cdot}001$.

during the entire trial. Ophthalmoscopically and angiographically, however, slight changes developed in the fundi of 3 patients receiving placebo and in 1 patient receiving cyclandelate (Table 1). These included the development of minimal hard exudates or some angiographical evidence of fluorescein leakage. The angiographical changes were observed in 2 placebo patients at the last examination, whereas the hard exudates were seen with the ophthalmoscope in 3 placebo-treated patients and in only 1 receiving cyclandelate. An overall clinical impression was, therefore, obtained of more marked progression of the retinal involvement in the diabetics not receiving cyclandelate.

SIDE-EFFECTS

Two patients complained of nausea. This was sufficient to provoke in 1 patient discontinuation of treatment and the consequent dropping out of the respective pair and its substitution with a new pair. It is interesting, however, to note that the second patient who complained of nausea was receiving the placebo capsules.

Discussion

The present trial has shown that cyclandelate in doses of 400 mg/capsule, 4 times daily, given for a period of 3 months, has significant beneficial effect upon the breakdown of the blood-retinal barrier which is present in the early stages of retinal involvement in diabetes. The use of vitreous fluorophotometry, a clinical quantitative method of evaluation of the permeability of the blood-retinal barrier, allowed the results to be subjected to statistical analysis. This showed that the progressive deterioration of the blood-retinal barrier observed in the diabetic patients receiving placebo capsules during the 3-month trial was arrested in the patients receiving cyclandelate. This beneficial effect of cyclandelate was particularly marked in the third month of treatment, when the levels of breakdown of the blood-retinal barrier decreased significantly, pointing to some recovery of the disease process, and suggesting even better results from prolonged periods of treatment. In a less clear manner the clinical impression obtained from ophthalmoscopy and fluorescence angiography agreed with the results obtained, showing an apparently more rapid progression of the disease in the placebo-treated diabetics. It remains now to be seen if these results can be confirmed by long-term studies and if the progression and development of the full picture of diabetic retinopathy and final loss of vision can be prevented by prolonged treatment with cyclandelate.

The results here reported showing a favourable effect of cyclandelate on the abnormal permeability of the blood-retinal barrier in the earlier stages of diabetic retinopathy are probably due to the protective action of the drug against hypoxia (Funcke *et al.*, 1974). It is to be recalled that an increase in retinal blood flow by direct action on the tone of the retinal vessels would not appear to have any beneficial effect, according to recent personal observations (Cunha-Vaz *et al.*, 1977), which showed an apparent direct correlation between increase in retinal blood flow and progression of diabetic retinopathy.

The demonstration of a beneficial effect of cyclandelate in early diabetic retinal involvement supports the work of Ditzel and Standl (1975a, b) and substantiates the hypothesis that fluctuations in tissue oxygen tension may be responsible for the retinal vascular complications in diabetes. Examination of the effect of this drug upon other vascular complications of diabetes may help to indicate if these variations in tissue oxygen tension are a general phenomenon of paramount importance in every vascular complication of diabetes or if they assume a particular significance in the retina, a tissue well known for its high metabolic needs.

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Localisation of macrophage lysosomal enzyme in experimental toxoplasma retinitis

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SUMMARY Rabbit retinal tissue experimentally infected with *Toxoplasma gondii* was processed for the lysosomal enzyme aryl sulphatase. Abundant lysosomal activity was found in lysosomal bodies of the infected macrophages. There appeared to be a lack of fusion of the lysosomal bodies with the phagosomes containing the organisms. Examination of the majority of macrophage vacuoles containing trophozoites failed to show consistently lead sulphide deposition for aryl sulphatase activity. By light microscopy 83% of 115 macrophage vacuoles containing the trophozoites of *T. gondii* showed an absence of lysosomal enzyme activity; 7% of the vacuoles containing the trophozoites were found to contain lysosomal enzyme activity. In the remaining 10% of the vacuoles containing the trophozoites of *T. gondii* the presence or absence of lysosomal enzyme activity could not be determined with certainty. The frequent absence of lysosomal enzyme activity within the phagosomes containing *T. gondii* organisms may be related to the parasite's ability to multiply and encyst in an intracellular locus. The abundant lysosomal enzyme activity in the lysosomal bodies within the cytoplasm of the infected macrophages may contribute to the cellular destruction of surrounding tissues when infected macrophages burst open owing to proliferation of the trophozoites.

Toxoplasma gondii is one of the commonest causes of retinitis (Jacobs *et al.*, 1956). Toxoplasma has the ability to survive and reproduce by endogeny (Hoare, 1972) in cytoplasmic vacuoles of cells, especially macrophages. It has been speculated that the inability of lysosomes to fuse with the macrophage phagosomes permitted the parasite to resist destruction by hydrolytic enzymes (Jones and Hirsch, 1972). Under these conditions rapid proliferation of organisms ruptured the infected cells.

In previous studies performed *in vitro*—i.e., tissue culture—the macrophage was precluded from interacting with normal tissue and serum elements such as lymphocytes, plasma cells, and complement which act *in vivo* to mediate cellular immunity and enhance macrophage phagocytosis. In this *in-vivo* study rabbit retinal tissue experimentally infected with *T. gondii* was processed for the lysosomal enzyme aryl sulphatase in an attempt to evaluate macrophage lysosomal enzyme activity and localisation during acute retinal infection and tissue destruction.

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Methods and materials

A 0·05 ml suspension of RH strain *T. gondii* containing approximately 10^6 free-swimming parasites per ml in Hanks solution, prepared by the method of Nozik and O'Connor (1965), was injected intravitreally at the equatorial region of the proptosed right globe of white New Zealand rabbits with a No. 27 gauge needle attached to a 1 ml tuberculin syringe.

The rabbits were killed after 5 days, immediately enucleated, and the infected globes immersed in a solution of 1·5% glutaraldehyde in a 0·1 M cacodylate buffer with 1% sucrose and 1% $CaCl_2$. The globes were cut in half at the equator and the vitreous was removed. The posterior retina containing most of the toxoplasma lesions was cut into 1-cm squares on a dental wax slab with a double-edge razor blade. The retina and choroid were dissected from the sclera with a small spatula and surgical blade under direct visualisation with a dissecting microscope. The dissected retina and choroid were futher divided into 3 to 5-mm squares. The specimens were constantly immersed in 1·5% glutaraldehyde in a cacodylate buffer during the dissecting procedure.

The tissue specimens were processed for the lysosomal enzyme, aryl sulphatase, according to the method of Goldfischer (1962) and subsequently treated with 2% ammonium sulphide (Holtzman and Dominitz, 1968). Controls consisted of tissue processed in a substrate-free medium.

On completion of incubation at 37°C for 1 hour in the enzyme substrate for aryl sulphatase the tissue was further fixed in a solution of 3% glutaraldehyde and 1% paraformaldehyde with 1% sucrose and 1% $CaCl_2$ for 1 hour.

After fixation all tissue specimens were stained *en bloc* with 1% OsO_4 in barbital-acetate buffer at pH 7·6 with 5% sucrose for 1 hour followed by 0·5% uranyl acetate in barbital-acetate buffer at pH 6·0 with 5% sucrose for 1 hour. The stained tissue was dehydrated in increasing concentrations of ethanol followed by propylene oxide and flat embedded in Araldite.

Thick sections for light microscopy were cut on glass knives and stained with Paragon* multiple stain.

Ultrathin sections were cut with a diamond knife, mounted on No. 200 gauge mesh copper grids, and viewed with an electron microscope.

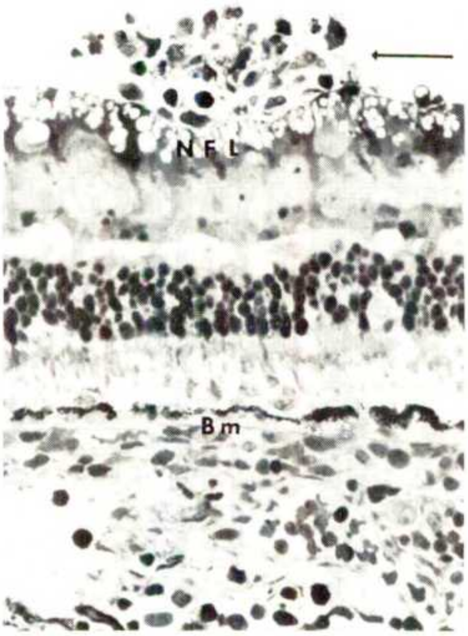

Fig. 1 *Cluster of macrophages* (arrow) *on the internal limiting membrane of the retina. The nerve fibre layer (NFL) appears vacuolated. The rest of the retina is intact. Bruch's membrane (Bm) separates the retina above from the choroid below (Araldite thick section with Paragon multiple stain;* ×400*)*

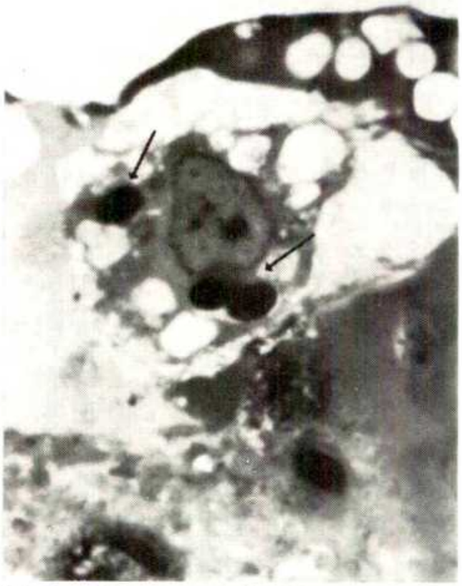

Fig. 2 *Higher-power field of the nerve fibre layer with a macrophage containing trophozoites of* T. gondii (arrows) *within the cytoplasm (Araldite thick section with Paragon multiple stain;* ×1000*)*

Results

PHYSICAL SIGNS AND GROSS PATHOLOGY

The infected rabbits were found to develop conjunctival injection with a crusty, straw-coloured exudate about 2 to 3 days after the inoculation with *T. gondii*. By the fifth day the rabbits appeared lethargic and somnolent.

Gross examination during the enucleation of the globe revealed no evidence of extension of infection into the sclera or beyond into the orbit. Examination of the retina showed areas of yellowish, pearl-shaped excrescences measuring 1 to 3 mm in diameter scattered over the posterior retina.

LIGHT MICROSCOPY

By light microscopy the pearly excrescences were found to be clusters of macrophages over the internal limiting membrane of the retina (Fig. 1). Higher-power examination of these macrophages showed the presence of intracytoplasmic, phagocytised toxoplasma trophozoites (Fig. 2). These organisms were found very commonly in macrophages throughout the retina, involving all layers. Occasionally they were found within the cytoplasm of glial cells.

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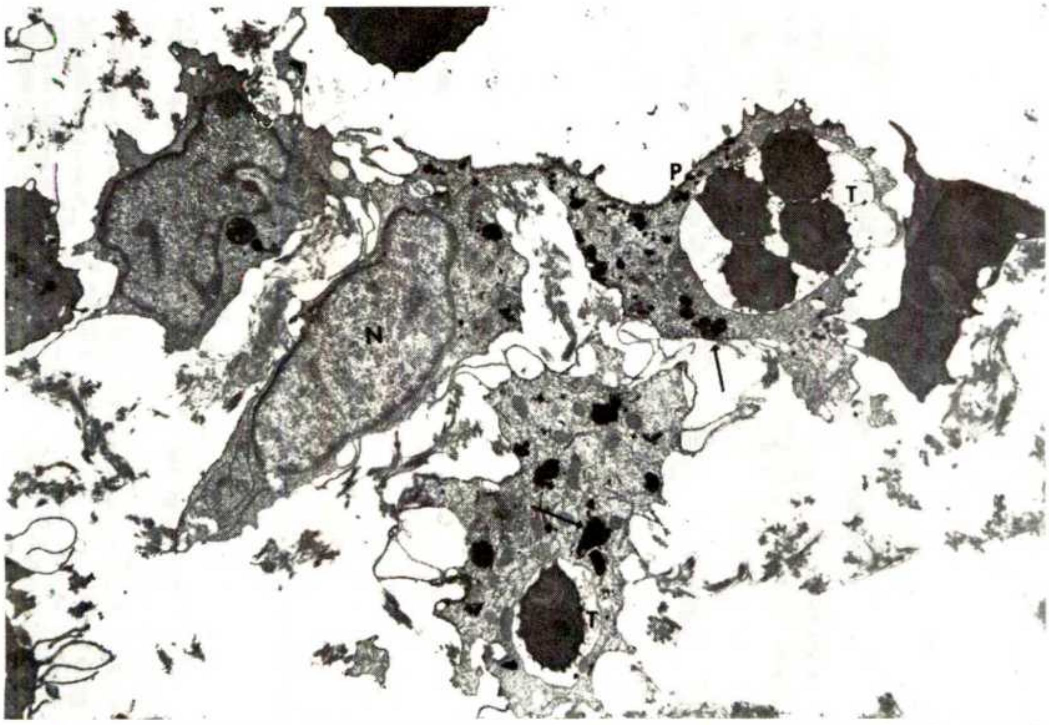

Fig. 3 *Macrophage with large nucleus (N) and pseudopodia (P) surrounding an aggregate of trophozoites of* T. gondii *(T) forming a cytoplasmic vacuole. The lower field shows a portion of a macrophage with a trophozoite (T) in a cytoplasmic vacuole. Dense lead sulphide deposits* (arrows) *are scattered throughout the cytoplasm of the macrophages. No lead sulphide deposition is noted within the vacuoles surrounding the trophozoites (Aryl sulphatase stained; OsO_4 and uranyl acetate;* ×2000*)*

The lesions of toxoplasma retinitis in the rabbit have been described previously (Yoshizumi, 1976). The optic nerve, ciliary body, anterior chamber, and cornea appeared grossly normal. The vitreous body appeared cloudy.

ELECTRON MICROSCOPY

Infected retinal tissue stained for aryl sulphatase activity was examined by electron microscopy with special attention to the macrophage vacuoles containing the trophozoites of *T. gondii*. The macrophages were identified by their narrow zone of surface ectoplasm, multiple pseudopodia forming large phagosomal vacuoles, the abundance of mitochondria, and lysosomal bodies in the cytoplasm (Lentz, 1971) (Fig. 3). Heavy deposits of lead sulphide were scattered throughout the cytoplasm of macrophages in lysosomal granules (Fig. 3). However, there was an absence of lead sulphide deposits within the majority of vacuoles containing the trophozoites of *T. gondii* (Fig. 4).

Some dense bodies within the cytoplasm of the trophozoites of *T. gondii* were found to be positive for aryl sulphatase precipitated lead sulphide deposits (Fig. 4).

Control retinal tissue incubated with substrate-free aryl sulphatase showed no specific areas of lead deposition.

Examination of some of the intracytoplasmic vacuoles containing the trophozoites in macrophages showed endoplasmic reticulum and mitochondrial aggregates surrounding the vacuolar membrane (Fig. 5). However, this was not a constant feature around most of the vacuoles containing the parasite.

LIGHT MICROSCOPY OF LEAD SULPHIDE DEPOSITS

One hundred and fifteen macrophage vacuoles containing the trophozoites of *T. gondii* and stained for aryl sulphatase activity were examined by high-power oil immersion light microscopy. Aryl sulphatase activity was identified by a dense brown lead sulphide precipitate visible by light microscopy.

Ninety-six of 115 or 83% of the intracytoplasmic macrophage vacuoles containing the trophozoites of

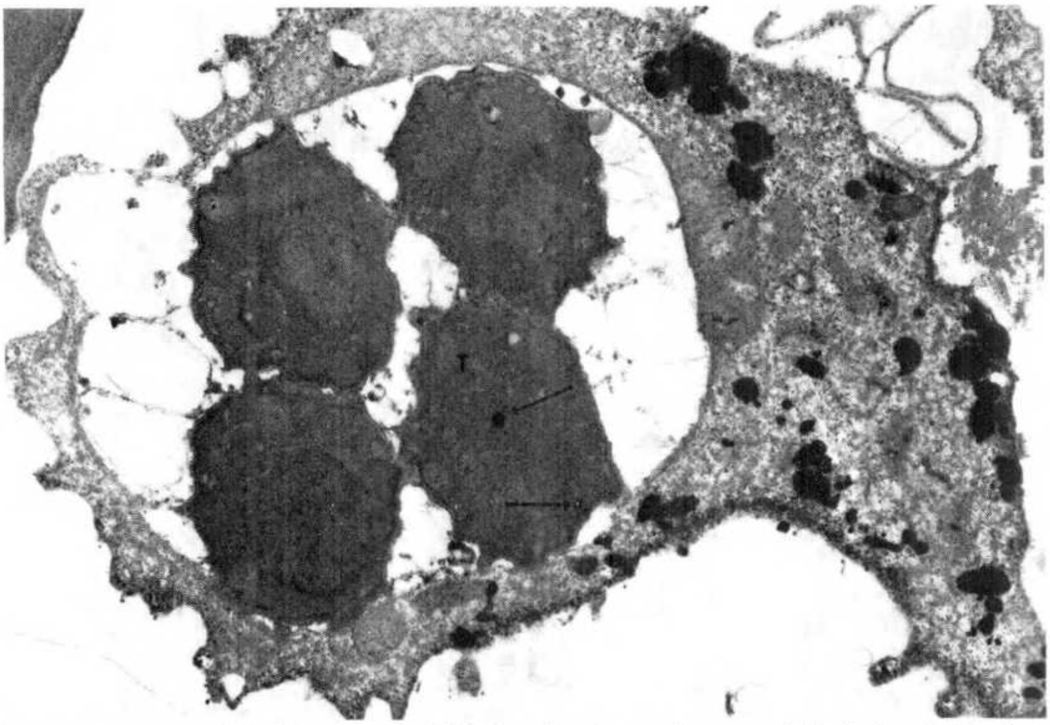

Fig. 4 *Higher-power field of Fig. 3. Lead sulphide deposition* (arrows) *is present within the dense bodies of one of the trophozoites (T) (Aryl sulphatase stained; OsO_4 and uranyl acetate;* × 6000*)*

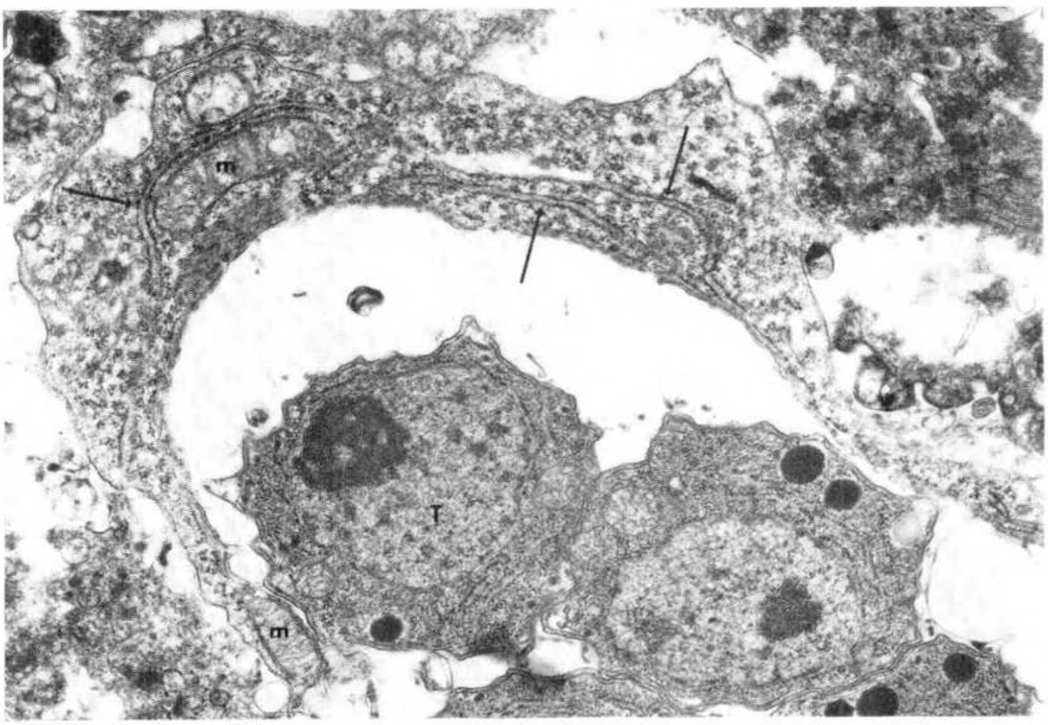

Fig. 5 *Trophozoites of* T. gondii *(T) are within the cytoplasmic vacuole of a macrophage. Surrounding the vacuole membrane are formations of endoplasmic reticulum* (arrows) *and mitochondria (m) (OsO_4 and uranyl acetate;* × 7500*)*

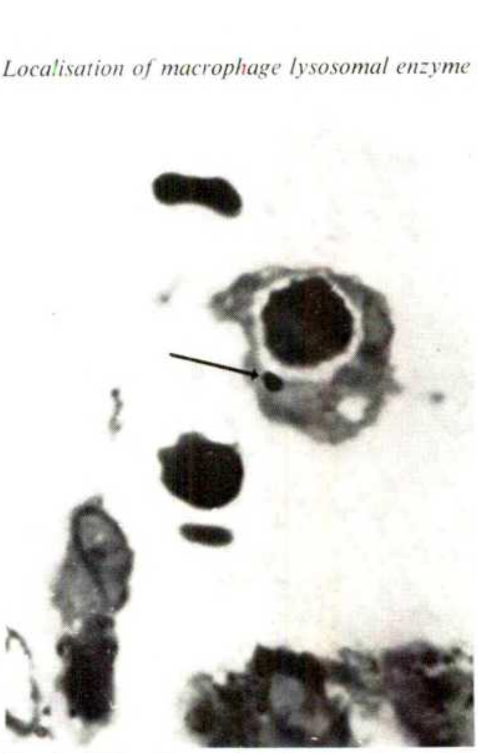

Fig. 6 *Light micrograph with a vacuole containing a trophozoite of* T. gondii. *Lead sulphite deposition is present in the cytoplasm of the macrophage* (arrow). *No lead deposition is present in the vacuole containing the parasite (Aryl sulphatase stained; OsO_4 and uranyl acetate; Araldite thick section stained with Paragon multiple stain;* × 1500*)*

T. gondii lacked lead sulphide deposits, though deposition was present elsewhere within the cytoplasm of the cell in lysosomal bodies (Fig. 6). Eight of 115, or approximately 7%, macrophage vacuoles clearly contained both lead sulphide deposits as well as the trophozoites of *T. gondii* and were indicative of aryl sulphatase activity within the macrophage vacuoles containing the parasite. Eleven of 115, or approximately 10%, macrophage vacuoles containing the trophozoites were equivocal for the presence of lead sulphide deposits and could not be clearly interpreted for aryl sulphatase activity.

Discussion

VACUOLE FORMATION

The formation and function of intracytoplasmic vacuoles in cells containing the trophozoites of *T. gondii* has been a point of considerable controversy. Earlier investigators (Lund *et al.*, 1961; Bommer *et al.*, 1969) have maintained that *T. gondii* is an obligate intracellular parasite that actively penetrates the cellular membrane to gain entry into the cell and subsequently, forms intracytoplasmic vacuoles as the site of reproduction. The lysosomes observed in the trophozoites in this study (Fig. 4) have been implicated in facilitating the penetration of the parasite into the host cell (Norrby *et al.*, 1968). In an electron microscopic study Zaman and Colley (1972) observed the anterior end of the *T. gondii* trophozoite penetrating the cell membrane. A membrane was formed around the parasite and the cytoplasm between the newly-formed membrane and the trophozoite dissolved, leaving the organisms in a clear 'parasitophorous' vacuole.

Jones *et al.* (1972) studied *T. gondii* trophozoites in HeLa cell, fibroblast, and macrophage tissue cultures at lowered temperatures to retard the entry process of the organisms into the cells and observed no evidence of cellular membrane penetration by the parasite. Instead, the formation of intracytoplasmic vacuoles containing the trophozoites of *T. gondii* appeared to occur through phagocytosis of the organisms by the cells. In the cases of parasitisation of HeLa cells and fibroblasts there was no evidence of destruction of the organisms within the vacuoles but, rather, reproduction of the parasites within the intracytoplasmic locus. In macrophages approximately half of the organisms phagocytised were interpreted to be digested and nonviable. The other half of the phagocytised organisms were interpreted to be viable and multiplied within the intracytoplasmic vacuoles.

LYSOSOMAL ENZYME LOCALISATION

A subsequent study by Jones and Hirsch (1972) investigated the localisation of lysosomal enzymes in macrophages in tissue culture infected with *T. gondii* and found that 96% of the vacuoles containing apparently viable organisms showed no evidence of lysosomal enzyme activity. 83% of the vacuoles containing degenerating trophozoites of *T. gondii*, distinguished on a morphological basis by darker staining and blurring of cellular structure, showed lysosomal enzyme markers.

In this study the lysosomal enzyme aryl sulphatase was examined in retinal tissue from rabbits experimentally infected with *T. gondii* to determine the localisation of the enzyme *in vivo* rather than in tissue cultured macrophages. It is well established that serum and cell mediated components of the immunological system act in concert with the macrophage in an attempt to destroy invading organisms (Stossel, 1974). Therefore an *in-vivo* study permits a more physiological evaluation of the fate of the phagocytised parasite in acutely infected retinal tissue rather than in tissue cultured macrophage studies.

83% of 115 macrophage vacuoles containing trophozoites of *T. gondii* processed for aryl sulphatase activity and viewed by light microscopy (Fig. 6) were found to show an absence of lysosomal activity. 7% of the macrophage vacuoles containing trophozoites were found to contain evidence of aryl sulphatase activity. The absence of lysosomal enzyme markers for aryl sulphatase in the majority of the macrophage vacuoles containing trophozoites was confirmed by electron microscopy. It was not determined whether the trophozoites within the 7% of macrophage vacuoles with evidence of aryl sulphatase activity were viable or degenerating *T. gondii* organisms. However, the frequent observation of macrophage vacuoles containing the trophozoites of *T. gondii* with absent lysosomal enzyme activity concurs with the findings of tissue culture study by Jones and Hirsch (1972).

Jones and Hirsch (1972) suggest that the viable trophozoites of *T. gondii* may produce a substance which prevents the fusion of lysosomal granules with the membrane of the phagosomes containing the parasite. Evidence for such a substance is still lacking. Another speculation put forward by those investigators is that the endoplasmic reticular and mitrochondrial 'overcoating' around the phagosome containing the trophozoites may block the fusion of lysosomal granules with the phagosome. Evidence for such an 'overcoating' by endoplasmic reticulum and mitochondria was observed in some cells in this study (Fig. 5), but it was not a consistent finding in all cells containing vacuoles with trophozoites and absent lysosomal enzyme (Figs. 3 and 4). Therefore such a mechanism preventing fusion of lysosomal granules with infected phagosomes remains speculative.

The cellular mediated immune response is one of the most significant mechanisms protecting the animal host during infection by the organisms of *T. gondii* (Frenkel, 1956; O'Connor, 1970). In cellular immunity the macrophage participates in the destruction of organisms by phagolysosomes (Stossel, 1974; World Health Organisation, 1969). The absence of lysosomal activity within the cytoplasmic vacuoles in a majority of the macrophages containing the trophozoites of *T. gondii* in acutely infected retinal tissue may be related to the ability of the parasite to invade, multiply, and encyst in an intracellular locus, and thus maintain a chronic infection characteristic of *T. gondii* retinochoroiditis.

Despite the inability of macrophages effectively to kill ingested trophozoites of *T. gondii* owing to the lack of fusion of the lysosomes with the phagocytic vacuoles the organism appears to elicit a vigorous lysosomal response (Fig. 4). This abundance of hydrolytic lysosomal enzymes, intended to kill the organism, may spill into the surrounding host tissue when infected cells burst due to proliferating organisms; thereby contributing to the intense cellular necrosis of surrounding uninfected cells typical of toxoplasma retinochoroiditis (Yoshizumi, 1976).

Two modes of tissue destruction are apparent. Firstly, the direct invasion and proliferation of the organism in an intracellular locus ruptures the host cell. Secondly, the spillage of hydrolytic lysosomal enzymes into the surrounding tissue may destroy cells that do not even harbour the organisms. Agents such as sulphonamides and pyrimethamine, which interfere with the metabolism of *T. gondii*, are employed to curb the first mode of tissue destruction, the proliferative phase of toxoplasma infection. Corticosteroids have been found to stablise lysosomal membranes (Weissmann, 1964) and may exert some therapeutic effect against the second mode of tissue destruction by reducing the spillage of hydrolytic lysosomal enzymes into the surrounding tissue.

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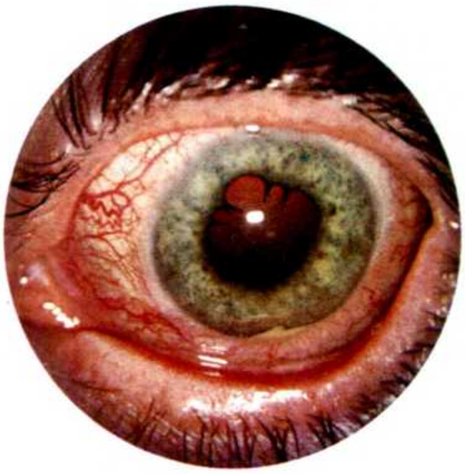

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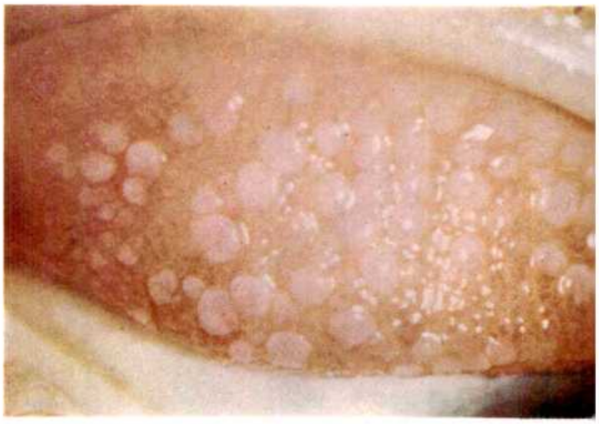
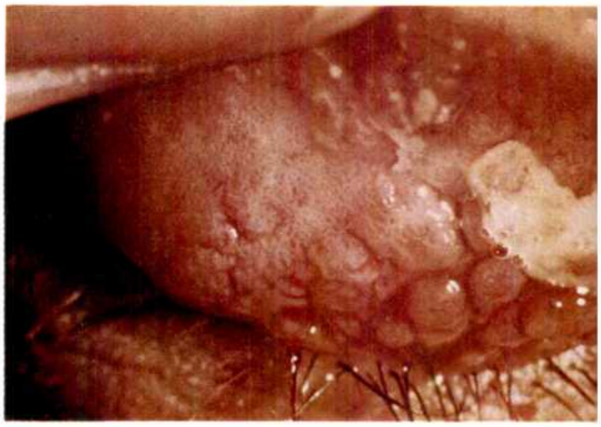
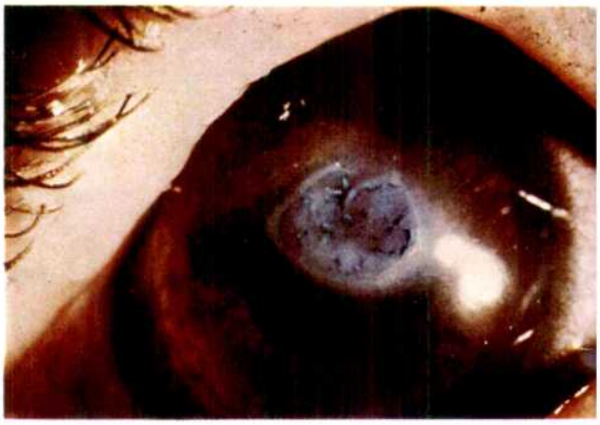


Right upper tarsus of adult patient with vernal kerato-conjunctivitis showing 'cobblestones' due to giant compound papillae.



Upper tarsal plate in active vernal disease. Note fine lace-like scarring and profuse mucopurulent discharge.



Indolent vernal corneal ulcer stained with alcian blue to demonstrate mucous deposition.

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Cryptococcal chorioretinitis: a case report

J. S. CHAPMAN-SMITH

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SUMMARY Chorioretinitis occurred in a young man whose long-standing cryptococcal meningitis had been identified and treated. In one eye spontaneous resolution had occurred. His case history and fluorescein angiograms are presented.

Cryptococcus neoformans (or *Torula histolytica*) is a yeast-like fungus producing systemic disease in man. Cryptococcosis (or torulosis) has a world-wide distribution. Infection is frequently by way of the respiratory tract. The organism is disseminated by the blood stream, particularly to the central nervous system, where a severe meningoencephalitis may develop. Before the introduction of amphotericin B in 1956 the disease was almost always fatal.

Many reports of cryptococcosis have appeared, but surprisingly few of ocular involvement. The eye may suffer the secondary effects of meningitis and raised intracranial pressure—papilloedema, optic atrophy, sixth nerve palsy, photophobia, and nystagmus (Khodadoust and Payne, 1969). The eye may be affected secondarily to orbital invasion, or the eye may be involved directly. Hiles and Font (1968) reviewed the literature to find just 9 cases of proved cryptococcosis of the eye. They added a case of their own. Khodadoust and Payne (1969) updated the count to 13 cases. Cameron and Harrison (1970) described 1 further case in which a mouse-virulent form of *C. neoformans* was identified in the patient's cerebrospinal fluid.

Case report

A 27-year-old white male was referred to his local general hospital in October 1969. He described a steadily increasing frontal headache, which developed over 2 weeks. Over several days before his admission he suffered from photophobia, was nauseated, and had vomited. He worked as a commercial artist, and over several years had worked in a tower inhabited by pigeons.

On his first admission he was noted to be febrile (38·9°C) and to have neck stiffness. *Cryptococcus neoformans* was isolated from his lumbar cerebrospinal fluid and cultured on Sabourad's agar.

On 5 November 1969 the patient was transferred to Fairfield Hospital in Melbourne. Relevant laboratory findings are listed: Cerebrospinal fluid: 32 cmH$_2$O pressure; *C. neoformans* present in Indian ink preparation. Leucocytes: 11·500 thousand/mm^3 ($11·5 \times 10^9$/l)—55% polymorphs, 32% lymphocytes, 0% oesinophils. Chest *x*-ray: a lesion present at the right lung base consistent with a toruloma. No bacteria or viruses were cultured from his throat, nasopharynx or blood-stream. No cryptococcus grown from pigeon faeces.

The patient began treatment on the day of his admission. Amphotericin B was administered as an intravenous infusion over 8 hours of each day. The dosage was 1 mg/kg per day, initially 5 days in 7, and later reducing to 3 days in 7.

The patient was transferred to St. Vincent's Hospital on 17 December 1969, where a right lobectomy was performed. The pathology report described a lesion surrounded by damaged lung parenchyma, in which both granulation and mucoid tissue were present. 'Innumerable cryptococci' were present within the mucoid material, and some cryptococci lay in alveoli adjacent to the main lesion. The lesion was diagnosed as toruloma of the right lung. The patient convalesced at Fairfield Hospital until 26 February 1970, when he was discharged clinically well. He was subsequently readmitted for several days each month for review of his general health and cerebrospinal fluid. Flucytosine tablets (8 g/day) were introduced to his treatment programme.

In March 1971 he had a generalised convulsion. He was prescribed phenytoin sodium tablets (100 mg) 3 times daily, which he still takes.

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In November 1971 he was admitted to the Alfred Hospital. His symptoms of headache and vomiting had recurred, and he had lost weight. Although his electroencephalogram and brainscan appeared normal, the air encephalogram showed dilatation of both lateral ventricles, suggesting moderate cerebral atrophy.

In early October 1972 he was admitted as an emergency to Fairfield Hospital and transferred to the Alfred Hospital. His headaches and vomiting were severe, he was wasted and unable to walk. Mentally he was vague and disorientated. Both optic discs had blurred margins, and peripapillary haemorrhages were seen. A large haemorrhage partly obscured the right disc and inferonasal retina. *C. neoformans* was again isolated from the cerebrospinal fluid. An air encephalogram showed grossly dilated lateral ventricles. Surgery was performed. A right atrioventricular shunt was inserted and connected to a Rickham subaponeurotic reservoir, which permitted subsequent administration of intrathecal amphotericin. His level of consciousness improved rapidly. He was transferred back to Fairfield Hospital, where he was given a trial of clotrimazole to supplement his drug therapy. This ceased after 1 week following gastrointestinal upset and inadequate blood and cerebrospinal fluid levels of the drug.

In November 1972 and June 1973 further obstructions occurred, and additional shunts were installed. His drug treatment stopped in January 1974 as his renal function was disturbed.

He remained symptom free until June 1976, when he noticed blurring in his left eye. He attended the Royal Victorian Eye and Ear Hospital on 23 July 1976. Both eyes appeared white and uninflamed. His right eye saw 6/5, his left could count fingers at 0·5 m. An elevated greyish-yellow lesion was visible ophthalmoscopically above and involving the left macula (Fig. 1). The corresponding nerve fibre layer was disturbed. The right fundus contained two irregular, flat, pigmented scars along the upper temporal vessels (Fig. 2). The optic discs appeared healthy in both eyes. The vitreous was clear.

The fluorescein angiogram (Figs. 3 and 4) shows an elevated lesion at the left macula, with dilated and aneursymal capillaries over its surface. The early retinal arterial phase shows leakage from these vessels and some subretinal staining. Extensive leakage of dye is apparent in the late picture. The lesions in the right fundus do not show any vessel leakage. The lesion in the left eye represents active chorioretinitis, those in the right eye old chorioretinitis. The blood picture was unremarkable, and serology was negative for syphilis, toxocara, toxoplasma, brucella, and leptospirosis.

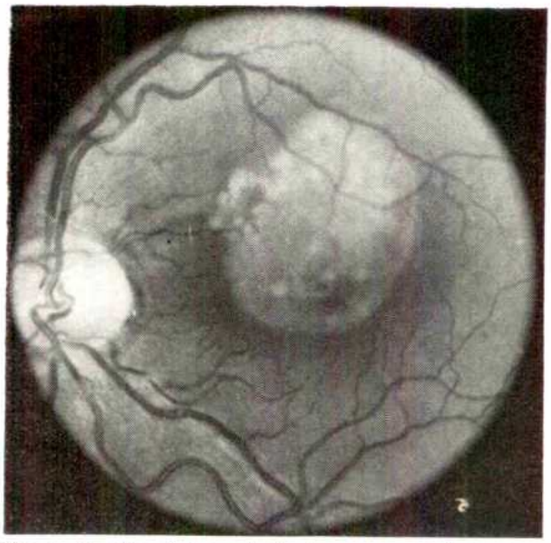


Fig. 1 *Fundus photograph showing active torulosis of the left eye*

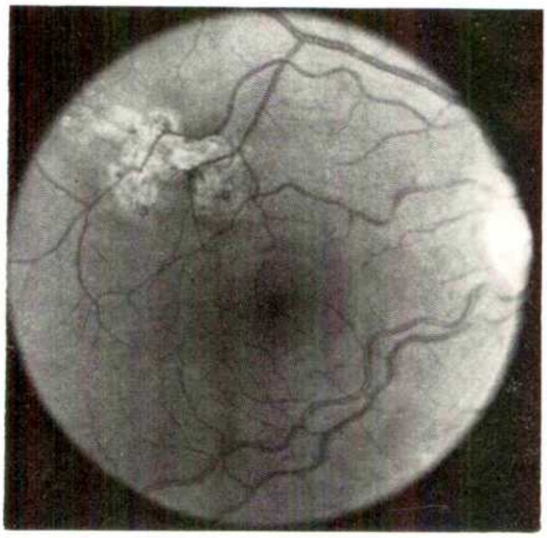
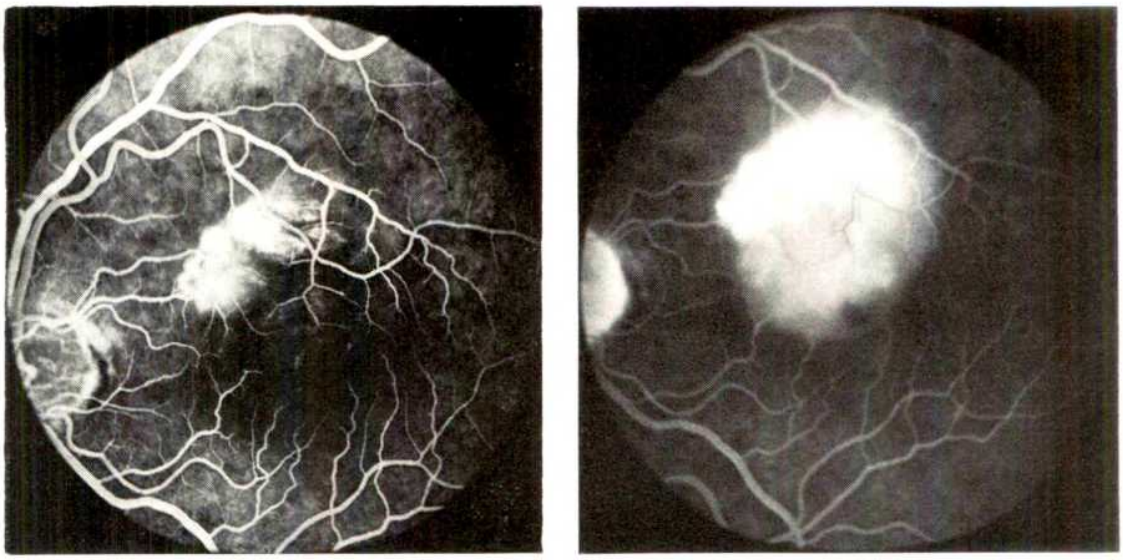


Fig. 2 *Right fundus showing scarring from previous chorioretinitis*

Argon laser was applied to the area of vessel leakage in the upper half of the macular lesions.

Discussion

Cryptococcus neoformans has been isolated from soil, fruit, and many animals. Its association with pigeons has been examined (Emmons, 1955) but 'no conclusive evidence exists that man has ever contracted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Figs. 3, 4 *Arteriovenous* (Fig. 3) *and late* (Fig. 4) *fluorescein angiograms of the left fundus*

the disease from infected birds' (Khodadoust and Payne, 1969).

In the cases reported so far chorioretinitis is the commonest form of direct eye involvement. Hiles and Font (1968) recorded that spontaneous resolution occurred in 1 eye of their patient. Uveitis, endophthalmitis, vitreous invasion by *C. neoformans*, and neuroretinitis have been reported (Khodadoust and Payne, 1969). The organism spreads to the eye either by the blood stream or in the meningeal sheaths surrounding the optic nerve.

A period of 6½ years elapsed between the onset of this patient's illness and the development of symptoms in his left eye. Hiles and Font (1969) noted a 2-year gap between meningitis and eye involvement in their reported case.

Treatment with amphotericin B has produced a 50% rate of cure in an American series (Okun and Butler, 1964). The risk of renal damage is considerable. Oral flucystosine has proved effective without significant adverse effects in some reports. Adequate cerebrospinal fluid levels can be achieved with oral administration (Stanton and Sanderson, 1974). Specific organism sensitivity to the drug should be demonstrated in the laboratory.

This patient, though relatively symptom-free, has regularly produced *C. neoformans* in his cerebrospinal fluid until his last examination in June 1975. His cerebrospinal fluid glucose remains low, protein high. Despite heroic treatment with amphotericin B, supplemented with flucystosine, the infection has not been eliminated. An uneasy truce exists between patient and pathogen.

I thank Professor G. W. Crock for the opportunity to examine his patient; Dr H. Newton-John of Fairfield Hospital for access to the patient's past records; and I acknowledge the photographic assistance of Mr J. Scrimgeour.

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Presumed choroidal naevi and sensory retinal detachment

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SUMMARY Two cases of choroidal naevus in patients with presenting complaints of blurred central vision and subsequent findings of abnormal retinal pigment epithelium (RPE) overlying the pigmented choroidal lesion are presented. Fluoroangiographic evidence of sensory retinal elevation in these areas is provided. Both cases were treated with low-intensity argon laser photocoagulation, with return of central vision without complication. The diagnostic importance of morphologically altered RPE, particularly lipofuscin pigment, overlying such choroidal tumours is stressed. A significant period of follow-up in each case is documented photographically.

Unusual morphological changes in the retinal pigment epithelium (RPE) overlying presumed choroidal naevi may be of significant diagnostic import. Histopathological changes in the retina overlying the naevus and corresponding field defects have been reported as associated findings in such cases (Hale *et al.*, 1965; Flindall and Drance, 1969). Presence of the yellow pigment lipofuscin on the surface of pigmented choroidal lesions has been reported as strongly suggestive of malignant melanoma (Smith and Irvine, 1973). We present two cases in which a choroidal neavus with obvious alterations in the RPE resulted in a sensory retinal elevation which extended into the fovea, causing a reduction in central vision. Argon laser photocoagulation was used to treat a demonstrable fluoroangiographic 'leak', and in both instances it flattened the retina and restored central vision. Follow-up photographs of the lesions at 4 years and 18 months respectively show no discernible change in the naevi.

Case reports

CASE 1

This 27-year-old White woman presented with a 2-week history of blurred central vision in the right eye. Visual acuity in the right eye was 20/20–3; in the left eye, 20/15. She had metamorphopsia on Amsler grid testing and a corresponding field defect on Goldmann perimetry in the right eye. A large, flat, pigmented lesion with a disturbance in the overlying RPE was observed temporal to the macula in the affected eye (Fig. 1*a*). Fluorescein angiography confirmed the clinical impression of an overlying serous retinal detachment (Fig. 1*c*). The clinical appearance of the sensory retinal elevation and visual disturbance remained unchanged for 9 weeks.

The area of leakage was subsequently treated with very low-intensity argon laser photocoagulation. Vision promptly returned to 20/15 and the scotoma disappeared. Four years later the clinical appearance and size of this lesion were unchanged (Fig. 1*b*).

CASE 2

A 29-year-old White woman was referred with findings of a flat, dark mass inferior and temporal to the disc in the left eye. The initial symptoms in that eye were visual acuity of 20/40, intense metamorphopsia, and a small field defect on perimetry conforming to the size and location of the lesion (Fig. 2*a*). The most striking clinical feature of this lesion was the obvious disturbance of the RPE in the form of a yellow pigment deposited on the surface of the choroidal lesion. This disturbance was associated anatomically with areas of 'leak' demonstrated by fluoroangiography (Fig. 2*c*). Persistence of these findings for 5 months prompted treatment with low-intensity argon laser photocoagulation. Vision improved promptly to 20/15, the subretinal fluid resolved, and her field defect disappeared. An 18-month follow-up fundus photo-

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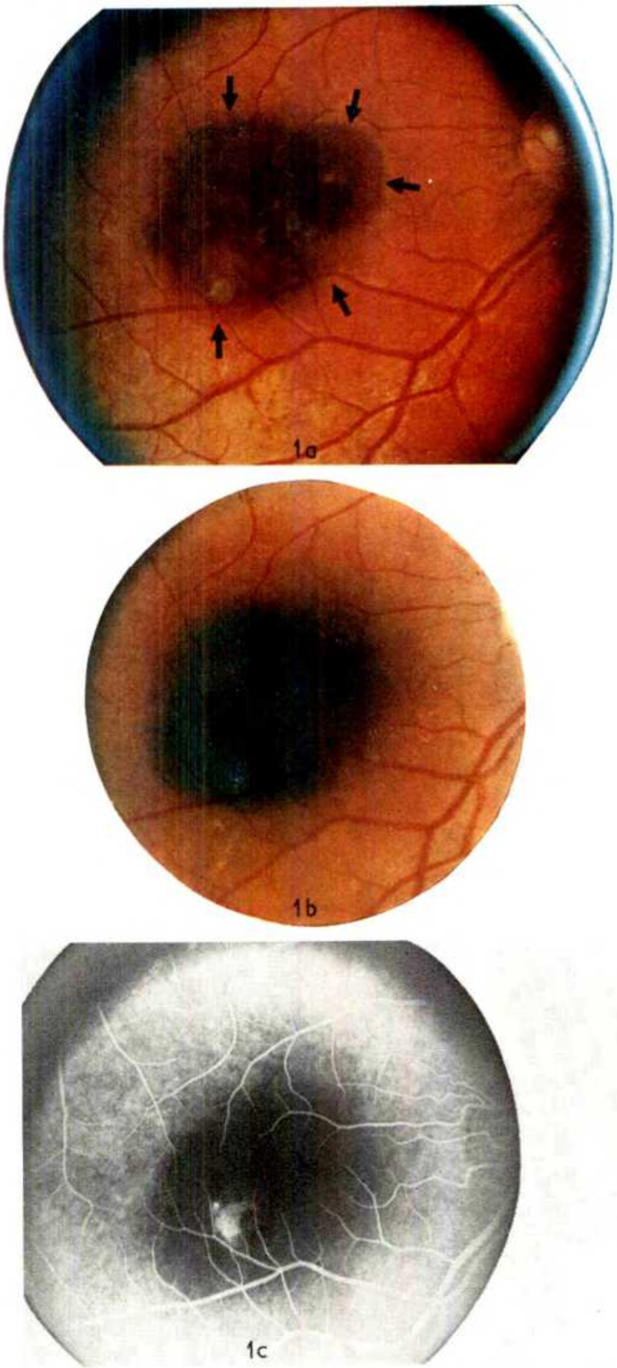

Fig. 1 (a) *Fundus photograph of pigmented choroidal mass and RPE disturbance in case 1 with arrows outlining extent of sensory retinal detachment.* (b) *This photograph taken 48 months later with different camera.* (c) *Morphological disturbance in overlying RPE is seen in central portion of naevus and corresponds to fluorescein leak during venous phase of fluorescein angiography*

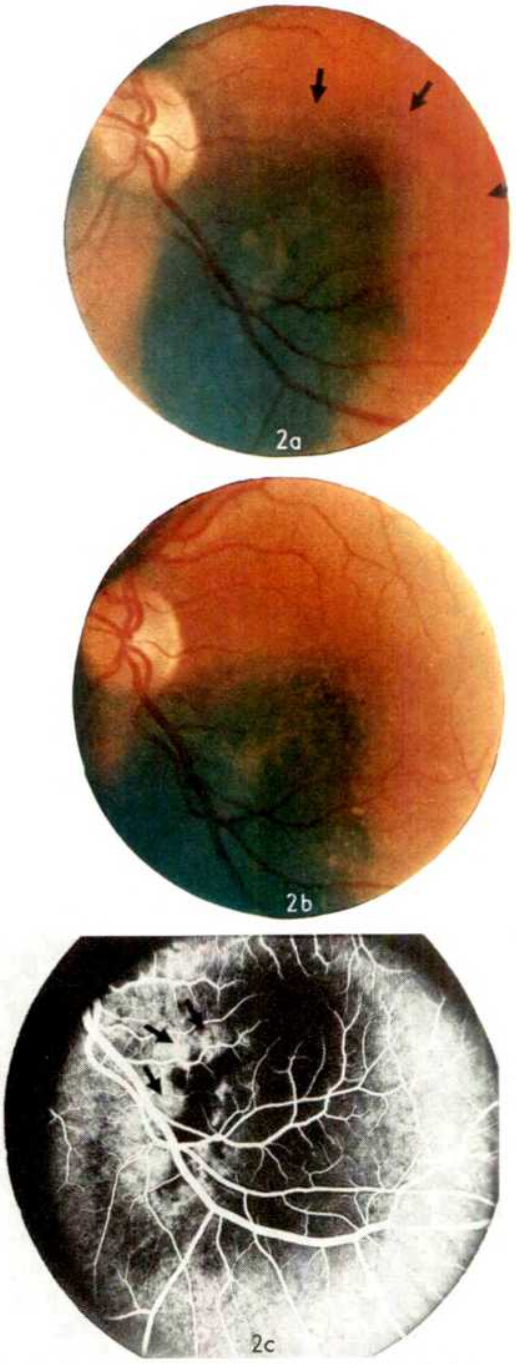

Fig. 2 (a) *Sensory retinal elevation associated with large pigmented choroidal mass, altered RPE, and orange pigment as it presented initially in case 2. Arrows indicate margins of detached sensory retina.* (b) *No discernible clinical change in appearance of mass or overlying RPE in 18-month follow-up.* (c) *Multiple areas of fluorescein leakage occurred around lipofuscin pigment, indicated by arrows* graph (Fig. 2*b*) indicates no change in the size or appearance of the lesion.

Discussion

In both patients the presenting complaint of metamorphopsia and blurred central vision led to the discovery of the choroidal lesion. In both cases fluorescein angiography showed the mechanism of visual reduction as a 'leak' in the area of altered RPE (Figs. 1*c*, 2*c*). The dense, homogeneous lipofuscin pigment in case 2 represents one type of RPE alteration and characteristically acts as a strong block to choroidal fluorescence. Only very light photocoagulation with an argon laser unit was required to flatten the sensory retina in each patient. In neither case was the clinical appearance of the naevus discernibly altered by the treatment.

With the incidence of choroidal naevi in the general population cited at 9%, Smith and Irvine (1973) have stressed the importance of attempting clinical differentiation between benign choroidal naevi and malignant melanomata. They have shown the importance of orange pigment overlying a choroidal tumour as a helpful criterion in this distinction. Shields *et al.* (1976) have recently pointed out that lipofuscin pigment is an alteration of RPE cells found in a variety of benign and malignant choroidal tumours, manifesting a differing clinical appearance but demonstrable with fluorescein angiography. The presence of severe RPE abnormalities over any pigmented choroidal lesion justifies a thorough evaluation and long-term follow-up. Both cases presented here, particularly the second case, are being followed up carefully with sequential fundus photographs, visual fields, and fluorescein angiograms.

We gratefully acknowledge the assistance of Dr J. D. M. Gass in evaluating case 1, and the kindness of Dr William Donald for referring case 2. Mr Marshall Tyler assisted with the photography and fluorescein angiography.

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Photoreceptor differentiation in retinoblastomas and its significance in prognosis

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SUMMARY Fleurette is an expression of photoreceptor differentiation and its presence is said to indicate a good prognosis. Twenty-four eyes from 22 cases of retinoblastoma sent to the Mitrani Foundation laboratory between the years 1964 and 1976 were reviewed histologically and clinically. The presence of differentiation in the tumour was not always associated with a good prognosis. The most important prognostic factor seemed to be the length of time the tumour is allowed to remain in the eye. The longer it remains the more undifferentiated the tumour cells become and the greater the probability that it will spread into the choroid and the optic nerve and out of the eye through the sclera and metastasise throughout the body. The presence of gliosis seems to improve the prognosis.

The prognosis of retinoblastomas has been thought to be related to the amount of differentiation of the tumour cells (Reese, 1963; Brown, 1966). The signs of differentiation taken into consideration have been the formation of fibrils and rosettes (Reese, 1963; Brown, 1966). Taktikos (1966) claimed that 'no significant relationship exists between the malignancy of retinoblastomas and the degree of their histological differentiation, which is unrelated to the mortality rate, the length of survival and the incidence of fatal complications'.

There is one point, however, on which both sides seem to agree—that is, that early diagnosis and prompt and appropriate treatment is the most important factor in the prognosis of the retinoblastomas (Taktikos, 1966).

Brown (1966) reported that a retinoblastoma first forms true rosettes which with time decrease in number and change into pseudorosettes or into anaplastic cells. Herm and Heath (1956) and Carbajal (1958) suggested that the longer the retinoblastoma is present the more undifferentiated it becomes. The conclusion is that it is not the degree of differentiation of the tumour cells but the length of time the tumour has been in the eye that counts in predicting the prognosis. In 1969 the fleurette, an expression of photoreceptor differentiation of the retinoblastoma cells was described for the first time (Ts'o *et al.*, 1969). This revived the question of the importance of histological differentiation in prognosis. While Ts'o *et al.* (1969) and Yanoff and Fine (1975) believe that the presence of fleurettes confers a better prognosis, Sevel *et al.* (1974) claim that it has no prognostic value.

To come to a better understanding of this controversial problem we reviewed our cases of retinoblastoma histologically and clinically.

Material and methods

Twenty-four eyes from 22 cases of retinoblastoma were sent to the Mitrani Foundation Eye Pathology Laboratory between 1964 and 1976. We have reviewed these histologically and clinically. At least five slides from each eye were histologically examined under high magnification (immersion). The whole surface of the tumour was covered in the examination. Stains used in addition to the routine haematoxylin and eosin included Masson's trichrome, PAS, and PTAH (phosphotungstic acid haematoxylin). We noted the type of tumour (retinoblastoma or neuroepithelioma); the kind and degree of differentiation of the cells, with special emphasis on the presence of fleurettes and glial cells; and the presence of calcification and necrosis, spread of the tumour out of the sclera into the choroid, optic disc, optic nerve, or anterior chamber. We recorded the ages at which the child was first examined and the tumour diagnosed; the age at which enucleation was performed; the occurrence

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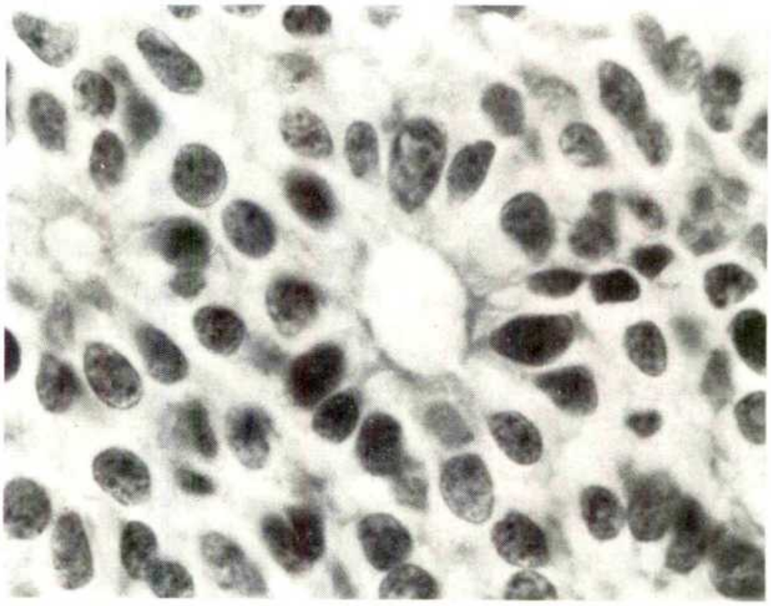

Fig. 1 *Rosette made up of undifferentiated cells.* × 1400

of scleral perforation during enucleation; the uni- or bilaterality of the tumour; and the familial incidence.

Results

HISTOLOGY

The tumour in all the 24 eyes was a retinoblastoma. We could see a few rosettes in 14 of them but not enough to merit calling the tumour a neuroepithelioma. In three cases there were those clear areas that Ts'o *et al.* (1969) considered characteristic of the presence of fleurettes. In all these areas we found fleurettes in different degrees of differentiation.

In general, the type of tumour cells varied from the very anaplastic type to the more or less differentiated photoreceptor or glial cell. Photoreceptor-like cells were seen mostly in true rosettes or around them Rosettes were formed either by cells with little cytoplasm and their nucleus near the limiting

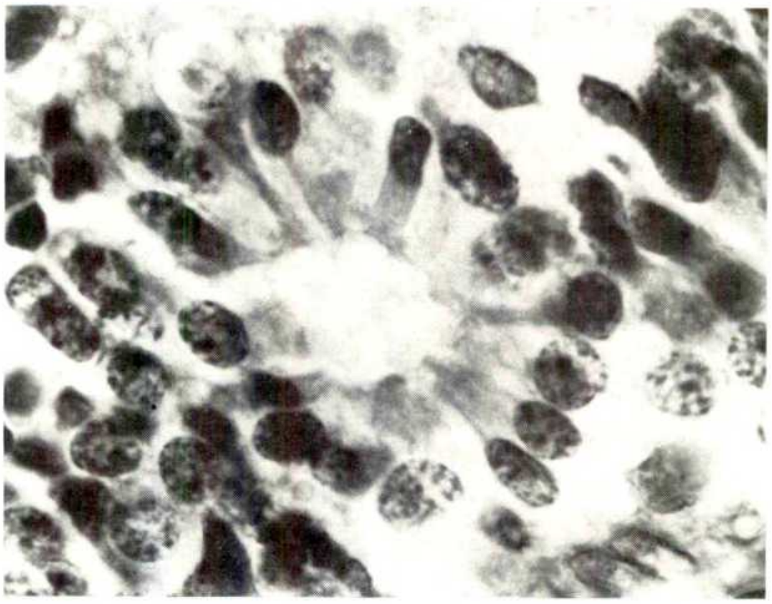

Fig. 2 *Rosette made up of partially differentiated tumour cells.* × 1400

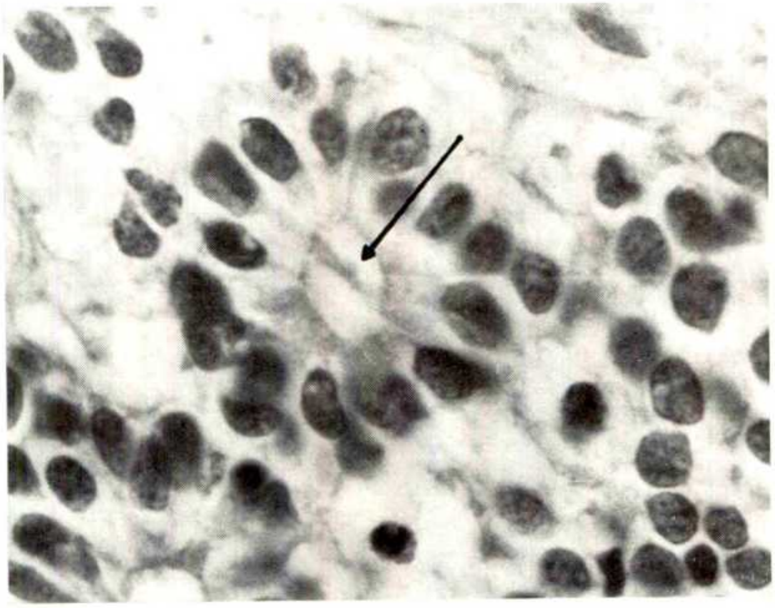

Fig. 3 *Rosette with one photoreceptor cell (arrow).* ×1400

membrane of the central lumen (Fig. 1), by cells with a relatively abundant cytoplasm not protruding inwards into the lumen (Fig. 2), or by cells showing cytoplasmic extensions into the lumen (Fig. 3). Incomplete rosettes were formed by rows of three to four cells parallel with each other, with a clear photoreceptor differentiation. Rosettes with all their cells showing photoreceptor differentiation were also present (Fig. 4). These rosettes showed no clear-cut limiting membrane and lumen centrally. There were photoreceptor-like cells arranged around a central line. These last three formations of cells showing an advanced degree of photoreceptor differentation could be called fleurettes. In addition we saw single photoreceptors among anaplastic cells (Fig. 5). Glial differentiation expressed itself as fusiform cells with long bipolar extensions arranged parallel with each other and as fibrillar areas around vessels. There were also fibrillar perivascular structures diagnosed as fibrosis with the Masson's

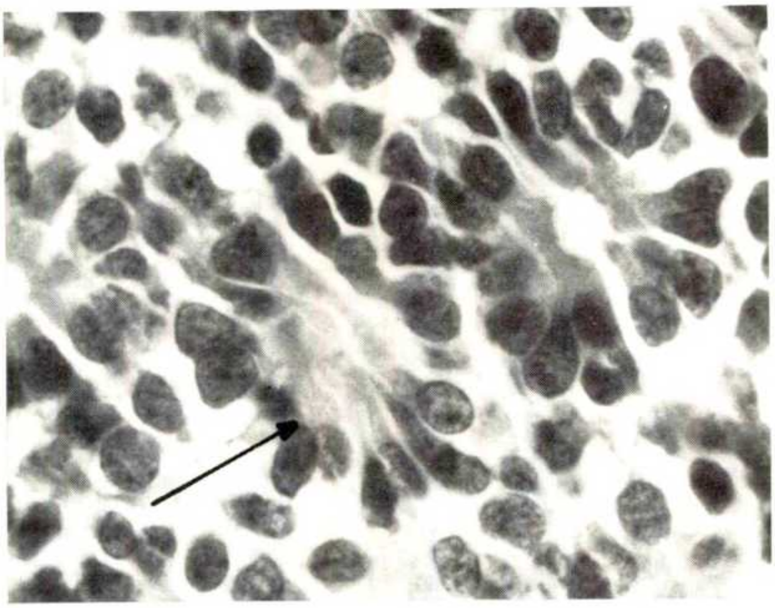

Fig. 4 *Rosette with all cells presenting photoreceptor differentiation (Fleurette) (arrow).* ×1400

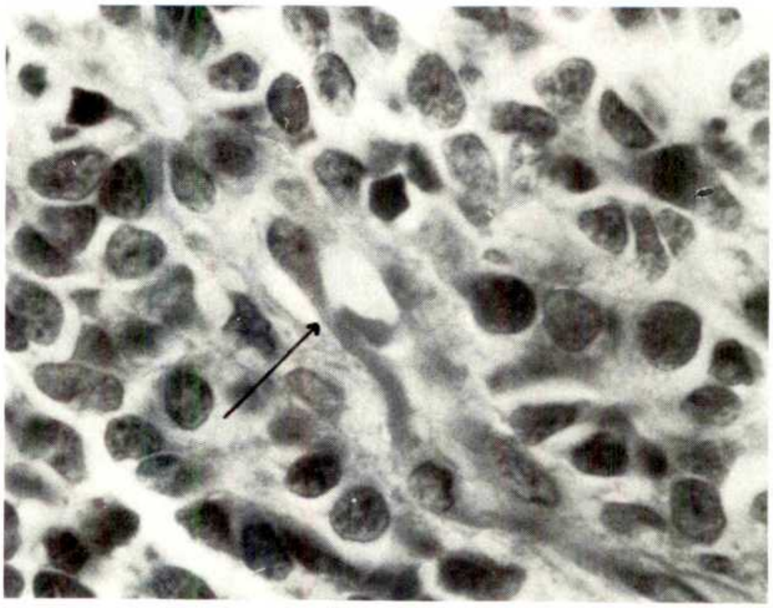

Fig. 5 *Single photoreceptor (arrow).* × 1400

trichrome stain. Numerous vessels had thickened walls or obstructed lumens (Fig. 6). There were large areas of necrosis and calcification.

Histology of irradiated tumours

Two of the 24 eyes were irradiated before enucleation. The tumour and the retina in each showed large areas of destruction, rosettes, loosening of cell connections and anaplastic retinoblastoma cells, and dispersion.

CLINICAL SURVEY

Seven of our 22 patients died and 15 are still alive.

In eight cases the child was first examined between 1 month and 1 year of age and in 14 cases between 1 and 5 years. In the first group three out of eight died one, $2\frac{1}{2}$, and four years respectively after enucleation. In the second group four out of 14 died during the first year after enucleation.

Usually eyes were enucleated one to two weeks after diagnosis. In five cases it was delayed for from

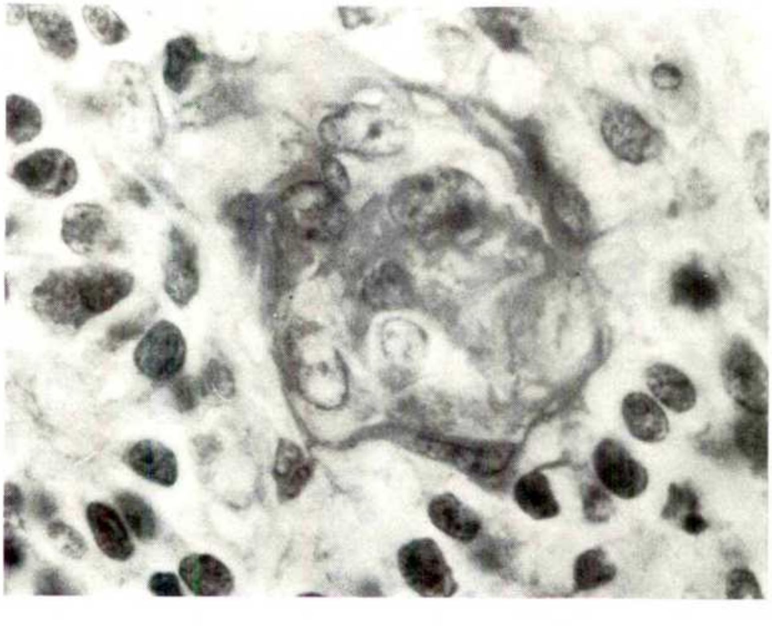

Fig. 6 *Occluded capillary in tumour.* × 1400

four months to four years after diagnosis. Four of these were unilateral cases and one was bilateral. All of them died in the first year after enucleation. Enucleation in those children whose retinoblastoma was diagnosed at the age of 1 to 4 years and died (four out of 14) had also been delayed.

Three of our 22 cases (24 eyes) were bilateral and in two of them we could examine both eyes. The remaining 19 cases were unilateral. In one bilateral case the patient died three years after the second enucleation. The patient in another bilateral case is still alive eight months after the second enucleation.

One case of bilateral retinoblastoma in which only one eye was enucleated and the second treated conservatively, is still alive six months after enucleation. In six out of the 19 unilateral cases the patient died 1½ to four years after enucleation. The follow-up of the remaining 13 cases extends from four months to four years.

Scleral perforation occurred in three cases. One of the patients died 2½ years after enucleation and the other two patients are still alive 10 years after enucleation.

No familial incidence was noted in our series of cases.

HISTOLOGY RELATED TO PROGNOSIS

Presence of rosettes Rosettes were seen in 14 out of the 24 eyes. They were present in four out of the seven cases in which the patient died.

Presence of fleurettes Fleurettes were seen in three cases. The patient in one case, a unilateral retinoblastoma, is still living 2½ years after enucleation. The patient in one case of a bilateral tumour died four years after enucleation. The patient in another bilateral case is still alive but follow-up has been for only eight months.

Presence of gliosis Gliosis was seen in three cases. The patients in all of them are alive eight months to eight years after enucleation.

Tumour spread outside the sclera The tumour had spread out of the sclera in six eyes pertaining to five cases. In four of them enucleation was delayed because the parents refused permission. All the patients died. The fifth case, a bilateral one, was diagnosed at the age of 1 month in both eyes. The first eye was operated soon after and the second 1½ years later after irradiation had failed to check the growth of the tumour. The child in this case is still alive but so far follow-up has not exceeded eight months.

Spread into the choroid This was observed in 12 eyes and 10 cases. In all of the seven patients who died the tumour had extended into the choroid. In the three who are still alive follow-up has not been for more than one year.

Spread into optic disc and optic nerve Spread only into the optic disc was seen in one case, and the patient is still alive one year after enucleation. Spread into the optic nerve was seen in 12 eyes and 11 cases. In all seven of the children who died the tumour extended into the optic nerve. The patients in the four remaining cases are alive and have been followed up for from eight months to three years.

Calcification and necrosis These were seen in all cases and were unrelated to prognosis.

Discussion

The term fleurette is applied to an elaborate form of photoreceptor differentiation of retinoblastoma cells. Some research workers think that the presence of fleurettes implies a better prognosis. Ts'o *et al.* (1969) reported no mortality in a series of eight cases of retinoblastoma with fleurettes followed up for eight years. Sevel *et al.* (1974), however, claimed that single photoreceptor cells or fleurettes were of no prognostic significance. We found the presence of fleurettes is not always associated with a good prognosis.

Fleurettes and well-differentiated single photoreceptors were seen in three cases. The patient in the unilateral case is still alive. Of the two patients with bilateral disease one is already dead and the other one, who has had both eyes enucleated and in whom both tumours were invading the sclera, choroid, and optic nerve, has been followed up for only eight months and is in a bad general condition. Interestingly, in these two bilateral cases fleurettes were seen only in the first enucleated eye and not the second, which was enucleated after unsuccessful irradiation.

The importance of rosettes in determining prognosis has been already evaluated. Tsukahara (1960) found no significantly greater mortality rate in patients with less differentiated tumours than in those with the well differentiated type. Reese (1963) ascribed a good prognosis to their presence. Our cases with rosette formation were too few in number to draw any conclusion.

The factor which seems most to affect prognosis is the length of time the tumour is allowed to stay in the eye—the longer the worse the prognosis. When seeing a child for the first time we cannot know how long the tumour has been present unless the patient is only a few weeks old. We may suppose, however, that the older the child the longer the tumour has been present. To this we could attribute the fact that the four out of the 14 of our children who had been examined for the first time when between 1 and 4 years of age died within one year after enucleation. But in these children enucleation was also delayed and this is a more likely reason for the bad prognosis. Indeed, in all five of our cases in which enucleation was delayed died soon.

The worsening of the prognosis owing to prolonged presence of the tumour may be perhaps because retinoblastoma cells become more and more undifferentiated with time (Brown, 1966). But accordingly our observations suggest that it is due mostly to the fact that as time goes on the tumour more likely to invade the sclera, the choroid, or the optic nerve. Spread of the tumour into the choroid and optic nerve caused general metastases in the body, which conservative treatment (irradiation and cytostatics) failed to check in five of our fatal cases. The only effect of the conservative treatment was to prolong the life of the child; it could not prevent a fatal outcome. We are unable to say whether tumour invasion of the anterior chamber had any prognositc significance in our cases.

The presence of gliosis might be meaningful. Indeed, our three cases who had gliosis are all alive. Gliosis is a sign of differentiation, and its presence might improve the prognosis. However, three cases is too few a number from which to draw any definite conclusion. Moreover, in none of them was there any extraocular spread of the tumour.

Unilaterality or bilaterality did not seem to be relevant to prognosis in our cases.

Scleral perforation during surgery is a rare complication but it might worsen the prognosis. Although the small number of our cases does not allow us to draw such a conclusion, we contend that scleral perforation during surgery disseminated tumour cells in the orbit and therefore adversely affected the prognosis.

In conclusion, we can say that photoreceptor differentiation in retinoblastomas does not mean a better prognosis. Rather it is the length of time that the retinoblastoma remains in the eye untreated, or inadequately treated, and extraocular spread of the retinoblastoma through the sclera and into the choroid and optic nerve that makes for a poor prognosis. It is two factors and not the presence of photoreceptor differentiation that must be considered in giving a prognosis.

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Comparison of ultrasonic and photographic methods of axial length measurements of the eye

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SUMMARY The axial length of 25 eyes was measured by the photographic method and by ultrasonography. The photographic measurements were consistently larger than the ultrasonic, but analysis gave a correlation coefficient of $r = 0{\cdot}8483$. The results suggest that the centre of rotation of the eye lies posterior to the anatomical centre of the globe. Using an empirical method of calculation and allowing for an error of $\pm 0{\cdot}3$ mm in the ultrasonic measurement, the photographic results were within $\pm 0{\cdot}5$ mm in 13 eyes and $\pm 1{\cdot}0$ mm in 7 eyes.

The photographic method may be helpful as a guide to the power of intraocular lens implants and for comparing axial lengths in population studies.

Recently Perkins *et al.* (1976) described a photographic method of measuring the axial length of the eye. Although this technique has clear advantages over the pre-existing methods in terms of simplicity and expense of equipment and its ease of application to children, the accuracy of the results in absolute terms was open to doubt. There was a high degree of correlation between the axial length measurements and the degree of ametropia, but there appeared to be an overestimate of approximately 3 mm when compared to the estimates of axial length by previous methods.

In the present study axial length measurements were taken by both photographic and ultrasonic techniques on the same eyes and the results compared.

Subjects and methods

25 eyes in 22 subjects were examined. 19 patients (21 eyes) were referred to the Ultrasound Department of Moorfields Eye Hospital for a routine ultrasonography, and 3 subjects (4 eyes) were volunteer members of the staff of Moorfields Eye Hospital. All had axial length measurements taken by ultrasound A-scan and before or immediately after this they had axial length photographs taken. For these latter measurements to be taken all the patients were required to have sufficient visual acuity to be able to fixate on the small central fixation spot which appears in the centre of the camera lens.

PHOTOGRAPHIC METHOD

The photographic equipment used was similar to that described by Perkins with a reflex camera mounted between 2 slit flashes (37° 28′ apart) on an arc centred on the focal point of the camera lens.

Calibrations

Before the study was undertaken the camera equipment was calibrated. Using various steel balls of known diameter mounted eccentrically by a precisely known amount and movable through an arc of 37° it was possible to mimic different sized human eyes and photograph them in a manner similar to that used in the subsequent study.

In the primary position the image separation on the film is directly proportional to the radius of curvature of the steel ball or cornea. Thus it was possible to arrive at a factor which allowed direct calculation of the radius of the corneal curvature from the film negative:

$$r = 2 \times f = n \times 0{\cdot}332$$

where r = radius of curvature (mm)
f = focal length for point source
n = number of scale divisions between the film images in primary position.

The distance from the focal point of the cornea to the centre of rotation of the eye can be calculated by allowing for camera magnification (× 1·88), scale differences on the negative (× 5), and the angle of deviation from the primary position (18° 44′), thus:

$$y = \frac{n}{1{\cdot}88 \times 5 \times 2} \text{ sine } 18^\circ\ 44' = \frac{n'}{6{\cdot}04}$$

where y = distance from focal point of cornea to centre of rotation (mm)
n' = number of scale divisions between the film images in deviated positions (37° 28′).

The theoretical length of the eye can then be

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found, namely, $l = 2y + 2f$ or $2y + r$, where l = axial length (mm).

Clinical measurements

The technique of photography used clinically was exactly as described by Perkins, and each patient had 2 keratometry photographs in the primary position and 3 'deviated' photographs looking at each flash in turn.

A-SCAN METHOD

A 10-MHz focused transducer was coupled to the eye by means of a bath containing Ringer's solution at 37°C. Eye movements were reduced to a minimum with the aid of a fixation light for the eye not under examination. The approximate position of the optical axis was located using the mechanical linear B-scan facility on the Moorfields system, and the transducer position then adjusted to attain maximum echoes from the anterior and posterior lens surfaces. Ocular distances along the optic axis were measured in microseconds and converted to millimetres using the following assumed velocity of sound propagation in ocular tissues at 37°C:

aqueous humour 1500 m per second (Begui, 1954)
lens material 1620 m per second (Begui, 1954)
vitreous humour 1520 m per second (Begui, 1954).

In those eyes with an irregular-shaped posterior segment (indicated on the B-scan) the length of the vitreous was taken as the maximum vitreous length along a horizontal axis.

The axial length measurements using this method are accurate to ±0·3 mm.

Results

From the calibration tests it was found that the accuracy of the 'keratometry' readings on the steel balls ranged from +0·01 to +0·22 mm (mean +0·09 mm) and the accuracy of the 'total length' measurements ranged from +0·65 to +0·37 mm (mean +0·48 mm). Thus the theoretical accuracy of the photographic method was within 0·5 mm.

The clinical measurements are summarised in Fig. 1 and Table 1. As the ultrasound A-scan measures from the anterior corneal surface to the anterior retinal surface, 1·4 mm has been added to the A-scan length in Table 1. This allows 1·15 mm for the scleral thickness and 0·25 mm for the choroidal thickness, which according to Duke-Elder and Wybar (1961a) is the average thickness of these structures.

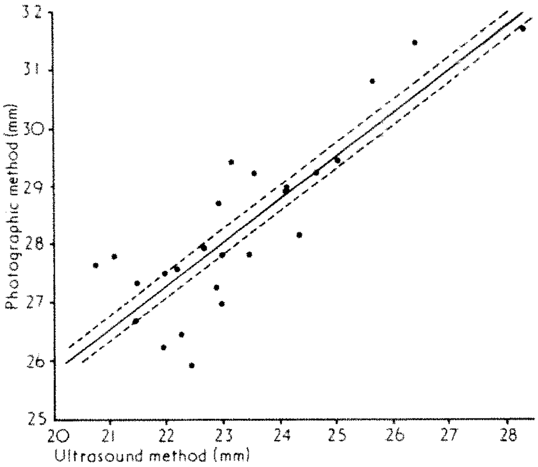

Fig. 1 *Axial lengths (abscissa) using the photographic method were derived from the theoretical calculation $l = 2y + r$ where l is the axial length, y is the distance from the focal point of the cornea to the centre of rotation and r is the radius of curvature of the cornea. Ultrasonic measurements are plotted along the coordinate. The dotted lines represent the possible error of the ultrasonic measurement: ±0·3 mm*

Table 1

A-scan + 1·4 mm	*Radius of curvature (r)*	*Distance from corneal image to centre of rotation (y)*	*Axial length (2y + r)*
22·12	7·80	9·93	27·66
22·47	7·96	9·93	27·82
22·85	8·04	9·33	26·70
22·87	8·10	9·62	27·34
23·32	8·00	9·11	26·22
23·35	7·64	9·93	27·50
23·59	7·80	9·89	27·58
23·63	7·48	9·49	26·46
23·81	7·80	9·06	25·92
24·04	7·64	10·15	27·94
24·27	7·88	9·69	27·26
24·31	8·58	10·05	28·70
24·37	7·60	9·69	26·98
24·37	7·64	9·27	26·18
24·53	8·30	10·57	29·44
24·83	7·96	9·93	27·82
24·93	7·88	10·68	29·58
25·50	8·14	10·39	28·92
25·52	8·50	10·24	28·98
25·73	7·96	10·10	28·16
26·05	7·94	10·65	29·24
26·42	7·92	10·76	29·44
27·04	8·30	11·26	30·82
27·80	8·30	11·59	31·48
29·70	7·60	12·04	31·68

It will be seen from the graph and the figures that the axial length as measured by the photographic method is consistently greater than that obtained by ultrasonography even when allowance is made for the thickness of the sclera. The difference varied from 1·81 to 5·35 mm (mean 3·54 mm). There is, however, a good correlation between the results from the 2 methods ($r = 0{\cdot}8483$) and the regression equation is $y = 0{\cdot}735x + 11{\cdot}15$, where y is the photographic measurement and x the ultrasound. If this equation is applied to the data, the difference between the 2 methods is less than ±0·5 mm in 10 eyes, between ±0·5 and ±1·0 in 8, between ±1 and ±1·5 mm in 6, and only exceeds this value (−1·7 mm) in 1 eye.

Fig. 1 shows the regression line and the dotted lines indicate lines corresponding to ±0·3 mm for the ultrasound method.

Discussion

In the photographic method what is actually measured is the radius of rotation of the corneal reflex about the centre of rotation of the posterior scleral segment (mean 10·5 mm). The calculation assumed that the apex of the cornea lies on the circumference of the arc of the circle described by the posterior sclera (Duke-Elder and Wybar, 1961b) and that the centre of rotation of the globe is midway between the apex of the cornea and the posterior pole. The present results suggest that this assumption is not correct and that the distance from the apex of the cornea to the centre of rotation is greater than that from the latter to the posterior pole by approximately 3·5 mm (see Fig. 2). As anatomical measurements all agree that the eye is almost spherical, it would seem that the globe does not rotate about its anatomical centre but about a point more posterior. The focal point of the cornea (radius of curvature ÷ 2) is situated very close to 3·5 mm from the apex of the cornea, and it was found empirically that a much closer correspondence between the ultrasonic and photographic methods could be obtained by calculating the axial length from the photographs by using the formula l = 2y + f, where y is the distance from the position of the corneal reflex to the centre of rotation and f is the corneal radius ÷ 2.

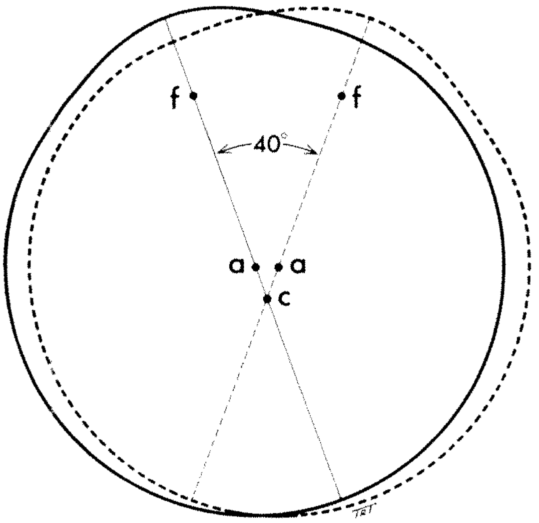

Fig 2. c *represents the centre of rotation of the globe,* a *the anatomical centre (i.e., a point midway between the apex of the cornea and the posterior pole), and* f *the focal point of the cornea. The distance* cf *is approximately equal to the distance from* c *to the posterior pole of the eye so that the axial length equals* 2cf *and half the radius of curvature of the cornea*

f = focal point of cornea; *a* = anatomical centre; *c* = centre of rotation.

Table 2

A-scan *+ 1·1 mm*	*2y + f*	*Difference*	*Difference ±0·3 A-scan*
22·15	23·77	+1·65	+1·35
22·47	23·68	+1·21	+0·91
22·85	22·68	−0·17	Within ±0·3
22·87	23·29	+0·42	+0·12
23·32	22·21	−1·11	−0·81
23·35	23·69	+0·34	+0·04
23·59	23·68	+0·09	Within ±0·3
23·63	22·72	−0·91	−0·61
23·81	22·28	−1·53	−1·23
24·04	24·13	+0·09	Within ±0·3
24·27	23·32	−0·95	−0·65
24·31	24·41	+0·10	Within ±0·3
24·37	23·17	−1·20	−0·90
24·37	22·36	−2·01	−1·71
24·53	25·29	+0·76	+0·46
24·83	23·85	−0·98	−0·68
24·93	25·30	+0·37	+0·07
25·50	24·85	−0·65	−0·35
25·52	24·72	−0·80	−0·50
25·73	24·18	−1·55	−1·35
26·05	25·27	−0·78	−0·48
26·42	25·48	−0·94	−0·64
27·04	26·67	−0·37	−0·07
27·80	27·33	−0·47	−0·17
29·70	27·89	−1·81	−1·51

Table 2 shows that in 17 of the 25 eyes the 2 measurements were within 1·0 mm, and in 9 eyes the results were within 0·5 mm. In 8 eyes the error was greater than 1·0 mm, and in 1 eye it was greater than 2·0 mm. If the limits of accuracy of the ultrasonography are taken into account the errors are as follows:

No. of eyes	*Error*
4	no difference
9	within ±0·5 mm
7	within ±1·0 mm
5	over ±1·0 mm

This empirical method of calculation is simpler than using a conversion table or graph based on the plotted values in Fig. 1, and although it may have no theoretical justification it does give results which agree with previous work.

Park and Park (1933) measured the centre of rotation in 14 subjects over a horizontal arc of movement from 38° temporally to 39° nasally. They found that the centre lay on the nasal side of the visual axis and moved on average from 12·95 to 14·73 mm behind the corneal apex. In the primary position it lay 13·84 mm behind the cornea. If, therefore, the corneal apex lay on the scleral circle, this would give an average axial length of 27·68 mm in these 14 subjects. Their refraction and axial lengths were not recorded, but it would seem likely that their subjects were emmetropic and it can be concluded either that the cornea protrudes in front of the scleral circle or the centre of rotation does not lie equidistant from the apex of the cornea and the posterior pole of the eye.

Given a centre of rotation of 13·84 mm behind the cornea and a corneal radius of 7·8 mm the average distance from the focal point of the cornea to the centre of rotation (y) would be 9·98 mm. Thus $2y+r$ would be 27·76 mm, i.e., about 3 mm too long, and $2y+f$ would be 23·86 mm, which is close to the average length of 24·15 mm quoted by Duke-Elder and Wybar (1961c).

During the course of this study 1 patient with nanophthalmos was measured by both techniques; she was not included in the results. She had a refraction of 18 dioptres of hypermetropia and an axial length by ultrasonography of 15·65 mm (right) and 14·79 mm (left). The photographic method gave lengths of 17·86 mm and 17·84 mm. It would seem that for a grossly short eye the photographic method becomes inaccurate perhaps because the posterior segment is aspherical and the sclera thicker.

The photographic technique measures axial length along the visual axis, and the ultrasonic technique used (for regular-shaped eyes) measures axial length along the optic axis. Jansson (1963) has shown that the difference in axial lengths along these axes is 0·1 mm. Several workers have described ultrasonic systems for axial length measurements along the visual axis. Giglio (1969) and Coleman (1969) have described systems operating at 20 MHz and said to be capable of accuracies in axial length measurements to within less than 0·05 and 0·03 mm, respectively.

Accommodation of eyes during the ultrasonic and photographic procedures may also account for differences in axial length measurements as measured by these 2 techniques.

The photographic technique is not accurate enough to be a refraction tool under normal circumstances, but it may have possibilities as a guide to the power of intraocular implants in cataract surgery. The photograph in the primary position gives an accurate keratometry reading, and thus a preoperative measure of corneal refractive power, although this may change postoperatively.

Using the empirical method of calculating the axial length would allow an estimate of the required refractive power of an implant lens to within 1·5 dioptres in 36% of cases and within 3 dioptres in 68% of cases.

One object of attempting to develop a simple method of measuring axial length was for use in population surveys, particularly with a view to the investigation of myopia, where ultrasonography techniques would be impractical. There are both theoretical and practical sources of error in the photographic method, and the ultrasonic method is clearly more accurate for an individual eye. However, it seems likely that for comparing axial lengths between emmetropes and myopes in a population any significant differences in axial length would be detectable by the photographic method. Its ease of application is particularly valuable for children, and as the error in any given eye will probably remain constant changes in axial length, e.g., with growth or the development of myopia, should be reliably measured. As the technique also provides a measurement of the radius of curvature of the cornea, the results would enable differentiation between ametropia due to radius of curvature of the cornea, axial length, or refractive power of the lens.

A cause of inaccuracy in the photographic method other than anatomical abnormality could be translatory movements on rotation of the eye. By taking the measurements in the horizontal plane the translatory movements due to the oblique muscles are minimal, but some lateral movement may occur. Head movements during photography have a similar effect, and this is definitely a major source of error. The 2 criteria for good photographic results are that the patient is able to see the fixation lights and that the head is held still during the time when the camera shutter is held open.

Inaccurate focusing of the images of the corneal reflex are another source of error, and it may be possible to devise optical methods for measuring the separation of the images without the necessity for photography. Experiments along these lines are in progress.

We should like to thank the Computer Department at the Institute of Ophthalmology for help with the statistical analyses and Mr Tarrant of the Department of Audio-Visual Communications for the diagram.

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Prevalence of refractive errors in adults over 40: A survey of 8102 eyes

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SUMMARY The prevalence of refractive errors was studied in an adult rural population. Of the 8102 eyes studied 18·4% were myopic, 57·1% were emmetropic, and 24·5% were hypermetropic. Mild myopia was commoner in males than in females, and mild hypermetropia was commoner in females than in males. There was increasing hypermetropia with increasing age, probably due to unmasked, latent hypermetropia up to the age of 70 years and to a true shift toward hypermetropia after the age of 70 years.

Most studies of the prevalence of refractive errors have concerned particular groups or races such as school children, students, army recruits, eye-clinic patients, Chinese, and Japanese (Duke-Elder and Abrams, 1970). We could find only one report in the literature in which Caucasian adults in the general population were examined (Witte, 1923).

In this paper we report the prevalence of refractive errors found in an adult population during a glaucoma screening programme.

Materials and methods

The members of the communal settlements of the Jezreel Valley (the Plain of Esdraelon) represent an ideal population for the study of the prevalence of disease. The population is intelligent and health conscious and enjoys free, comprehensive health care at a single medical centre which is also responsible for preventive medicine. Each settlement has a clinic and a nurse, greatly facilitating the organisation of preventive medicine programmes.

All necessary ophthalmic care, including spectacle examinations, is performed by the ophthalmologists and opticians of the Central Emek Medical Centre. It may be assumed that every adult member of the population has been refracted at least once and is wearing an appropriate distance correction unless he is emmetropic. Literacy is 100%, most men hold a driver's licence, cinema going is a national pastime, and films have subtitles. The members do not pay for their spectacles, and an outsider would probably be amazed at the large number of spectacles in their possession—tinted and clear, for reading and for work, bifocals and trifocals.

A population census was compiled with the help of the nurse at each settlement who recorded each member's identity number, sex, year of birth, country of birth, and occupation. The details were entered into a computer.

A team of 2 or 3 ophthalmologists visited each settlement and all members aged 40 years or more were invited for examination as part of a glaucoma screening programme. The members were asked to bring along their distance spectacles and after confirming in each case that the spectacles presented were, in fact, for distance, they were measured with a focimeter; the prescription was recorded on a special form and was later entered into the computer.

The survey was performed over a period of two years, and during the same period a detailed diagnosis was recorded and entered into the computer for all members of the same population who attended the eye clinic of the Central Emek Medical Centre. The computer program and the glaucoma survey have been reported elsewhere (Hyams and Isenberg, 1977; Isenberg and Hyams, 1977; Hyams, 1977). At the conclusion of the survey, a print-out was obtained showing the diagnosis, personal details, and spectacle correction of all subjects who attended for glaucoma screening.

Results

4639 people attended for glaucoma screening. 588 people were not included in the study because they had glaucoma, ocular hypertension, cataract, or aphakia in one or both eyes. Monocular patients were also excluded. 8102 eyes of 4051 patients were

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therefore included in the study; the age and sex of these subjects is shown in Table 1.

The distribution of refractive errors among the 8102 eyes is shown in Table 2 and in Fig. 1. 57·1% of the eyes were emmetropic. Myopia was present in 18·4% of the eyes examined, but if myopia of up to 1·0D is excluded the prevalence of myopia was 11·6%. The most myopic refraction was −30D. Hypermetropia was present in 24·5% of eyes, but if hypermetropia of up to 1·0D is excluded the prevalence of hypermetropia was 15·2%. There was a slight shift towards myopia in males compared to females: 9·8% of eyes of male subjects and 4·9% of eyes of female subjects had myopia of 1·25 to 4·0D; 10·4% of eyes of male subjects and 16% of eyes of female subjects had hypermetropia of 1·25 to 4·0D (see Fig. 2).

Table 1 *Age and sex of 4051 subjects*

Age in years	*Males*	*Females*	*Total*
40–49	488	505	993
50–59	563	602	1165
60–69	606	696	1302
Over 69	280	311	591
Total	1937	2114	4051

Table 2 *Prevalence of refractive errors in 8021 eyes*

Refraction	*Prevalence, %*		
	Males	*Females*	*Males and females*
−9·25D to −30·0D	0·7	0·4	0·6
−6·25D to − 9·0D	1·0	1·2	1·1
−3·25D to − 6·0D	5·1	3·9	4·4
−0·25D to − 3·0D	13·8	12·6	12·3*
Emmetropia	58·9	54·1	57·1
+0·25D to + 3·0D	18·2	25·2	22·1†
+3·25D to + 6·0D	2·1	2·3	2·2
+6·25D to + 9·0D	0·2	0·3	0·2
			100·0

*Including 6·8% with myopia of up to 1·0D
†Including 9·3% with hypermetropia of up to 1·0D

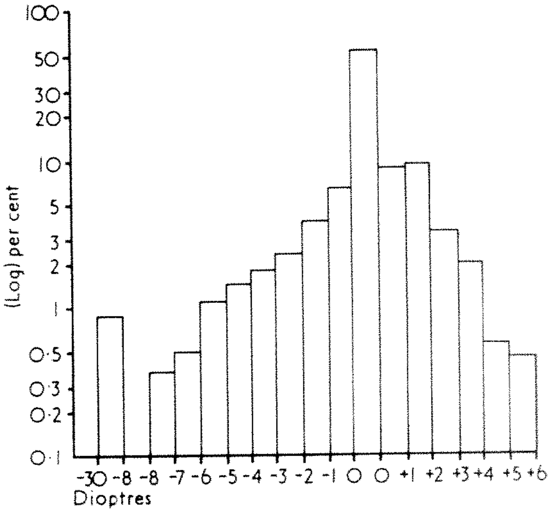

Fig. 1 *Histogram showing the prevalence of refractive errors in 8102 eyes. Prevalence in per cent on logarithmic scale*

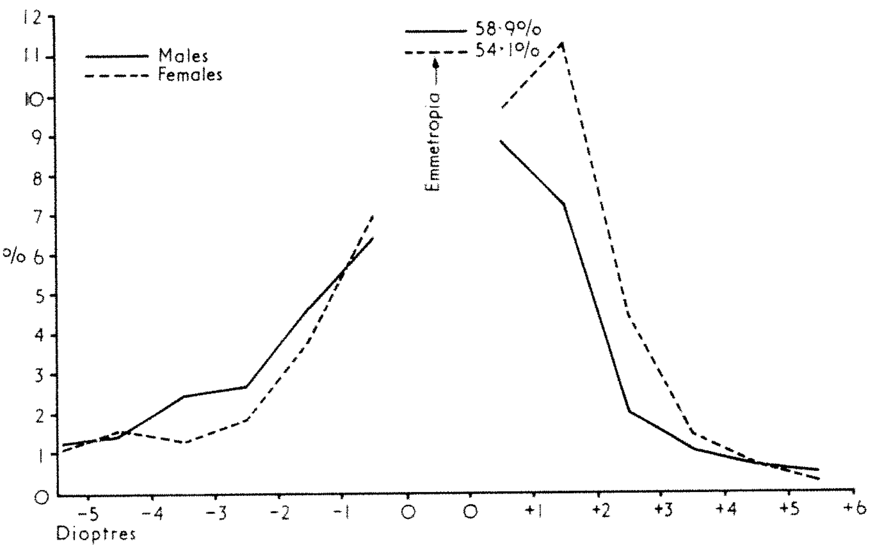

Fig. 2 *Prevalence of refractive errors in males and females*

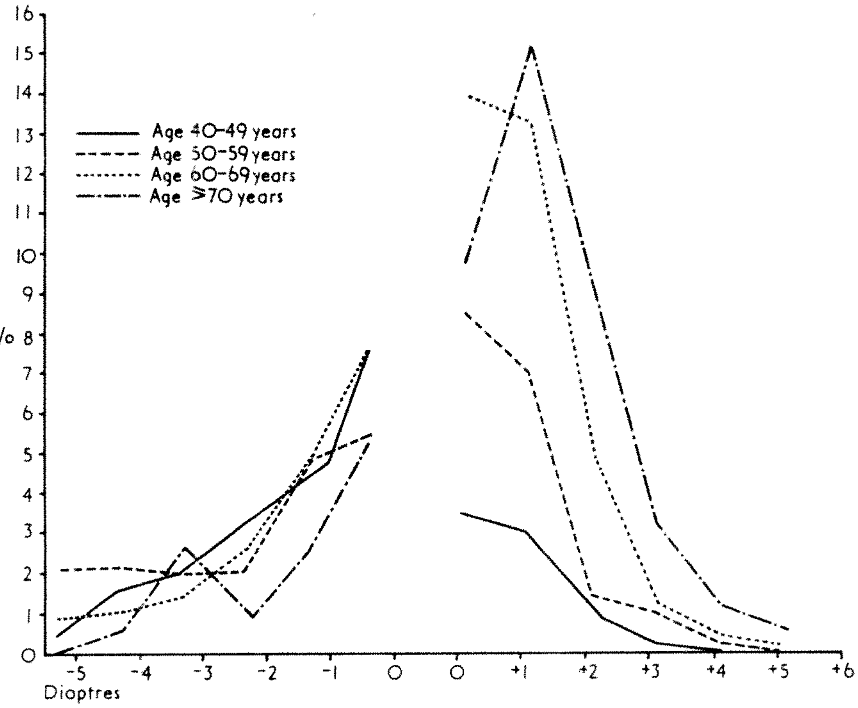

Fig. 3 *Prevalence of refractive errors in 4 different age groups*

There was more hypermetropia with increasing age. Fig. 3 shows that the prevalence and degree of hypermetropia increased progressively after the age of 40 years. The prevalence of myopia did not change from the age of 40 to the age of 70 years but decreased after the age of 70 years. These trends were demonstrated separately for males (Fig. 4) and for females (Fig. 5) with the exception of females over the age of 70 years.

Discussion

A knowledge of the prevalence of refractive errors is essential when studying the incidence of various disease processes which are related to the refractive state, such as retinal breaks, retinal detachment, and angle-closure glaucoma.

The prevalence of myopia reported by various authors varies between 0·12 and 3·8% in Africa, 2·4 and 27·8% in Europe, and up to 70% in China, Japan, and Egypt. The findings of previous authors are summarised in Table 3, which is adapted from Duke-Elder and Abrams (1970) and from Av-Shalom *et al.* (1967). The large variation in the reported prevalence of myopia is at least partly due to the fact that various groups of subjects were investigated.

The present study is almost unique in that it was

Table 3 *Prevalence of myopia reported by various authors—adapted from Duke-Elder and Abrams (1970) and Av-Shalom* et al. *(1967)*

Author	*Country*	*Year*	*Subject*	*Prevalence myopia, %*
Holm	Congo	1964	General population	0·12
Av-Shalom	Africa	1967	Children	1·7
Hertz	Liberia	1964	Students	2·0
Pipov	Russia	1931	Children	2·4
Douning	USA	1945	Army recruits	3·16
Clarke	UK	1924	Eye-clinic patients	4·5
Av-Shalom	Africa	1967	Eye-clinic patients	3·8
Goldschmidt	Denmark	1968	Children	9·5
Sorsby	UK	1960	Young men	10·7
Betsch	Germany	1929	Adult clinic patients	12·5
Witte	Germany	1923	General population	13·8
Kronfeld	Germany	1929	Adult clinic patients	14·6
Undgren	Sweden	1953	Children	17·0
Thompson	UK	1919	Children	18·8
Sato	Japan	1964	Children	27·0
Harman	UK	1936	Eye-clinic patients	27·0
Hess	Germany	1894	Children	27·8
Takahashi	Japan	1939	General population	31·0
Li	China	1920	General population	53·0
Sato	Japan	1964	Young adults	67·0
Rasmussen	China	1936	Young adults	70·0
Girgis	Egypt	1948	Children	70·0

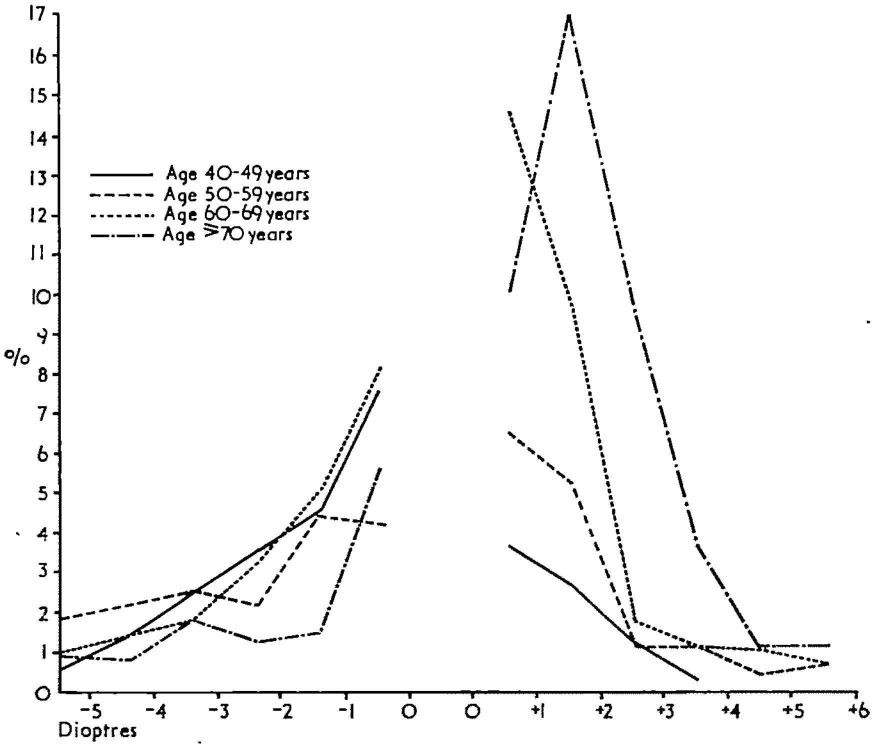

Fig. 4 *Prevalence of refractive errors in eyes of male subjects; 4 different age groups*

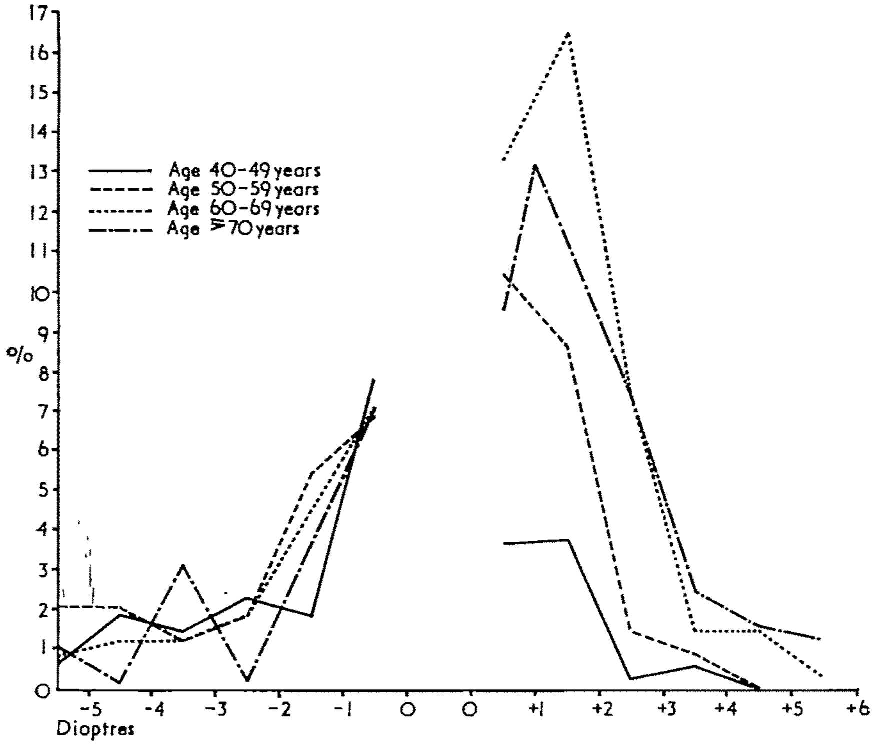

Fig. 5 *Prevalence of refractive errors in eyes of female subjects; 4 different age groups*

performed on an adult Caucasian population. Over 95% of the subjects are of Eastern European birth or origin; all of them are literate and work in agriculture or related services.

Our finding of increasing hypermetropia with increasing age is probably due to unmasked, latent hypermetropia up to the age of 70 years. Increasing hypermetropia accompanied by decreasing prevalence of myopia after the age of 70 years is probably due to a true change in the refraction of the ageing eye, associated with a reduction of lens curvature and changes in the relative refractive power of the lens cortex and nucleus (Duke-Elder and Abrams, 1970). The preponderance of females among hypermetropes and of males among low myopes has not been published.

We hope the results presented above will provide a better basis for studies of the incidence of refraction-related conditions. For example, the prevalence of retinal breaks in eyes with myopia of more than 1 dioptre in subjects over the age of 40 years in Israel is 16·9% (Hyams and Neumann, 1969). The number of myopic eyes with retinal breaks in subjects over the age of 40 years is therefore 2 200 000 × 11·6 × 16·9/10 000 = 43 129 eyes. The inadvisability of treating such eyes is obvious when one knows that there are fewer than 170 primary retinal detachments in myopic eyes in Israel per year (Michaelson *et al.*, 1974). The present study may also form a basis for comparison with other groups in which the prevalence of myopia seems to be higher or lower than the average.

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Book reviews

Photoprocesses, Photoreceptors, and Evolution. By J. J. WOLKEN. 1975. Pp. 317, 152 figs, tables, bibliog. Academic Press: New York (£11·90)

'And God said, let there be light: and there was light. And God saw the light, that it was good'. Then He brought forth living creatures—first plants, then fishes and birds, then land animals, and finally man.

Light has been associated with life since its origin and all forms of life are dependent for their living on the absorption of solar energy. To utilise this energy effectively photoreceptor systems developed so that a process of photosynthesis could convert light energy into chemical energy for cellular metabolism. The vast scale of the process is seen in the surmise that 100 billion tons of organic compounds are thus synthesised each year. The response of living creatures from phototropism in plants to phototaxis in motile organisms to vision in the higher types is discussed. As these phenomena evolved from bacteria and fungi to plants and animals a vast variety of structures is utilised, from dermal sensitivity to specific eye-spots and finally the retina, as well as several specific molecules constituting pigments or pigment-systems to absorb the light energy. The author has described the structures of these—porphyrins, chlorophylls, carotenoids, flavins, and other types—integrating the researches of a number of authorities with his own. Although morphological distinctions in the organs thus developed among plants and animals are marked, the interesting conclusion is reached that a common molecular basis for all photoreceptor systems exists despite the multitude of these structural variations. The phenomena of photoperiodism and the nature of photochemical memory as well as of bioluminescence are also discussed.

The book is ambitious and its territory wide, but the author has undoubtedly succeeded in his task. The reader will require to overcome any antipathy he has to chemical formulae, but the book contains a vast store of information skilfully presented and has a plentiful supply of beautiful illustrations, including some fascinating photomicrographs and a useful and up-to-date bibliography for further reading. STEWART DUKE-ELDER

Advances in Vitreous Surgery. Edited by A. R. IRVINE and C. O'MALLEY. 1976. Pp. 720, figs, tables, refs. Charles C Thomas: Springfield, Illinois ($51)

This book has been compiled from the contributions to a conference on recent advances in vitreous surgery held at the University of California Medical Center in 1974. Unlike so many publications which arise from symposia, the editors here have contrived to produce a volume which can be fairly described as excellent. Despite there being 50 contributors the work is comprehensive and well balanced.

The 63 chapters are divided into 12 parts. The first two parts deal with vitreous structure and examination of the vitreous body and the patient. Parts three and four deal with the surgical techniques of both the anterior and pars plana approaches. The next three parts deal almost entirely with different aspects of modern instrumentation. Parts 8–11 deal with different aspects of vitreous surgery which are related to specific diseases, apart from vitrectomy. In part 12 there are conjectures about future developments, with special emphasis on ultrasonic instruments.

It was provoking though stimulating to find that so many of one's ideas for the advancement of instrumentation, like cryofixation of the globe, have passed beyond the stage of debate to be put into practice, though it was pretty obvious from the proliferation of different instruments, both for vitrectomy and for the management of intraocular haemorrhage, that scope for improvement remains wide open.

Of particular interest also were the excellent papers on massive vitreous retraction (OKUN, Scott) or massive preretinal proliferation (Machemer) and the six chapters on the various aspects of diabetic retinopathy, which continues to be the main source of vitreous problems and the greatest stimulus to further work.

A. D. MCG. STEELE

Management Complications in Ophthalmic Plastic Surgery. Edited by D. B. SOLL. 1976. Pp. 379, figs, refs. Aesculapius Publishing Co: Birmingham, Alabama, USA ($55)

This elegantly bound, printed, and illustrated volume from the USA, written by some 20 ophthalmologists and plastic surgeons, attempts, once again, to chart the no-man's land between ophthalmology and reconstructive surgery. Unhappily, it is only a partial success, and rather an expensive one at that. This must be largely due to the ponderous and unmanageable title under which the many distinguished contributors have been obliged to write. 'Complications' in this field of orbital, lachrymal, and palpebral reconstruction are almost always the result of the wrong operation or of the right operation done badly, and one has great sympathy with the authors whose only real meassage (which does emerge through the repetitive and contrived passages on complications) must be 'do it properly'.

Of the 17 chapters, all of which provide useful information for the newcomer to this field, two may be singled out for comment. That on orbital fractures is excellent, in that it is succinct, well written, and practical in its approach. By contrast the chapter on eyelid reconstruction is sadly inadequate. Operations of this sort account for much of the surgery in this field, and the real problems (and the complications) arise only when large defects, exceeding 50% of the full thickness of an eyelid, must be made good. The reader will search this chapter in vain for guidance in the repair of such larger defects. Total reconstruction of an eyelid receives no mention at all, and the large and beautifully executed drawings, which occupy much of the space in this chapter, merely depict the meticulous repair of relatively trivial defects. Incredibly there is no mention anywhere in the book of burn injuries of the eyelids, which seems a curious omission from a work of this sort.

One should add that, in spite of this critical review, the book contains much practical information and should be a useful addition to the textbook literature in this field.

ROBIN BEARE

Optometry Handbook. By LEROY RUBIN. 1976. Pp. 198, figs, tables. Butterworth Group: London (£8·90)

The *Optometry Handbook* has chapters on visual acuity, ophthalmic optics, prescription design, ophthalmic lenses, refraction and analysis, contact lenses, low vision, and pharmacology. Each chapter is a compilation of statistical data drawn from various sources which will be particularly useful to manufacturers and opticians but of little value to ophthalmologists unless they specialise in ophthalmic optics. Of some interest to ophthalmologists would be the section on pharmacology, which lists and cross-references many drug preparations used locally and systemically that have an effect on vision. The other statistics given still keep to the obsolete American foot measurements with regard to acuity, and therefore will be of less value to British and Continental readers.

M. RUBEN

Advances in Ophthalmology. Vol. 34. Edited by E. B. STREIFF, H. SAUTTER, and M. J. ROPER-HALL. 1976. Pp. 226+8, 65 figs., refs. Karger: Basel (DM 129)

The subjects covered in this volume are the ageing of the lens, persistence and hyperplasia of the primary vitreous, the mechanisms of amblyopia, the use of laser interferometry to measure retinal visual acuity, and finally the papers presented at a symposium on lasers and the anterior segment of the eye.

Professor Jean Nordmann's publications on the biochemistry of the lens span an astonishing 50 years from his thesis in 1926 to the present very welcome review of the ageing process in the human lens and the pathology of senile cataract. The normal lens continues to grow throughout life, though the rate of growth slows down with age. In all types of senile cataract the axial cortex is thinner than in a normal lens of the same age, and there is a deficiency of fibrogenesis and protein synthesis before opacities occur. All attempts to involve extralenticular factors in the genesis of cataract have failed except perhaps for hyperglycaemia, and it seems that cataract is a local condition resulting from changes in the lens alone. Protein synthesis is slowed down, particularly with regard to glutathione, but the importance of this factor is unknown. Attempts to substitute the deficient glutathione have not given satisfactory results, and the most hopeful therapeutic possibilities are to find substances which can penetrate the lens to activate protein synthesis. The requirements for substantiating claims for any method of treatment are clearly outlined. Drs M. Gonvers, R. Faggioni, L. Zografos, and C. Gailloud from Lausanne review the literature and present a case of persistence of the primary vitreous, concluding that this is a condition comprising a number of entities previously considered as separate. The possibility of an aetiological connection with retrolental fibroplasia cannot be excluded.

Dr G. K. von Noorden reviews the mechanisms of amblyopia as revealed by animal experiments which have shown that amblyopia is accompanied by alteration in the response of neurones in the striate cortex and by structural changes in the lateral geniculate body. It is likely that the bilateral amblyopia in such conditions as congenital cataract results from deprivation of form vision, whereas in unilateral amblyopia from squint there is an additional factor resulting from abnormal binocular functions.

Retinal function can be tested by forming interference fringes on the retina with a low-power laser. This subjective test is independent of refraction and can be used to assess function in patients with cataracts. The instrument used by Drs Rassow and Wolf is described, and a comparison of the results with the final visual acuity after cataract extraction was encouraging.

The symposium on lasers and the anterior segment was held in Hamburg in April 1976 and was concerned with experimental and clinical studies on the use of lasers for iridotomy and trabeculotomy. The experimental studies dealt with the biochemical reactions in the eye after laser irradiation, including metabolic changes and the liberation of prostaglandins, threshold damage levels for the structures of the anterior segment, and experimental results with a dye laser.

The clinical discussions confirmed that laser iridotomy is now well established as a satisfactory procedure, and although it is possible to burn a hole with the argon laser alone it is probably better to use the argon laser to produce initial stromal damage and to complete the iridotomy with a pulsed laser. The clinical value of laser trabeculotomy for chronic simple glaucoma is still controversial, although good results were claimed from using a Q-switched ruby laser. But the fall in intraocular pressure in successful cases is limited, suggesting some degree of obstruction in outflow channels beyond the trabeculum.

As is usual with this series the volume is well produced and illustrated and provides an excellent review of current work in the fields represented.

E. S. PERKINS

Grundlagen und Methodik der Ophthalmodynamometrie, Ophthalmodynamographie, Temporalisdynamographie. By D. ULRICH. 1976. Pp. 152, 58 figs., 21 diagrams, 33 tables. Georg Thieme: Leipzig (no price)

In comparison with other blood vessels in the body the retinal vessels have two advantages for measurement of blood pressure; they can be easily seen and they are enclosed in the corneo-scleral envelope. This means that it is relatively easy to increase the external pressure acting on the retinal vessels and to observe the effect. Perhaps it is the frequent reminder, during routine ophthalmoscopy, of the ease of observation of the retinal vessels which continues to urge ophthalmologists to try to improve the technique and the interpretation of the results of ophthalmodynamometry and related procedures. In relation to the effort, however, the yield of information about the ocular circulation seems to be low, although it may be possible to make certain deductions about the state of the carotid and cerebral circulations. The duration of the effort to develop ophthalmodynamometry can be judged from the brief historical review in this book, which shows that work on the human eye can be traced back to the first decade of this century.

Early chapters in this book deal with the relevant anatomy (including the numerous variations in arterial origins and branchings), physiology, and hydrodynamics of ophthalmodynamometry, and there are some useful diagrams to help the reader through this part. There follows a section on the different techniques which have been described. The instruments themselves vary according to whether they raise the intraocular pressure by pressing on the eyeball or by exerting suction on it. Also, in some techniques, force is exerting on only a small part of the eyeball (for example, with Bailliart's ophthalmodynamometer), while in others (for example, Hager's so-called ophthalmodynamography) the force is transmitted to all the orbital contents. It is rightly stressed that one has to consider what is being measured. With the usual methods of ophthalmodynamometry it is the pressure in the ophthalmic artery, but with Hager's procedure it is probably the pressure in the internal carotid. A technique of dynamography of the temporal artery is also described.

The author makes clear that there are many sources of error and a number of problems in interpreting the results, and he discusses these matters fully. A great deal of factual material is presented. For example, there are 15 pages of graphs giving the relationships between pressures in the ophthalmic artery as determined by ophthalmodynamometry and brachial arterial pressures, and the corresponding relationships for pressures measured by ophthalmodynamography and in the temporal arteries. This mass of information is further complicated by the need to give systolic, mean, and diastolic pressures, and by the change in relationships according to the posture of the patient.

Dynamography differs from dynamometry in that it gives a recording of the form of the pulse wave and is applicable to the orbital contents or the temporal arteries. The recording of the pulse wave gives the opportunity for further analysis of haemodynamic events in terms of pulse volume, pulse duration, and the speed of rise and fall of the pulse wave. All these matters receive attention. Recent developments offering more hope for future advances are also mentioned; these include the use of ultrasound and the Doppler effect, and the combination of dynamometry with recordings of the visual evoked response.

On the whole the contents of this book amount to a careful and painstaking presentation of the known facts of ophthalmodynamometry and related techniques, but one is left with a feeling of disappointment that it is not possible to demonstrate a greater contribution to practical clinical problems. J. GLOSTER

Ocular Electrophysiology: A Clinical and Experimental Study of ERG, EOG, and VER. By J. BABEL, N. STANGOS, S. KOROL, and M. SPIRITUS. 1977. Pp. 172, 145 figs., 21 tables. Georg Thieme Verlag: Stuttgart (DM69)

The field of electrophysiology as applied to the eye has seen significant advances in recent years, and workers in this field are now familiar with the beautiful recording technique of these particular authors at the Geneva eye clinic. This book, which is translated from the French, is a clinical and experimental study of the electroretinogram, the electro-oculogram, and the visually evoked response based on work done over the past 10 years. The notable feature of the work is the development of the technique of averaging to produce these electrical responses. In particular, the form of the electroretinogram is portrayed very accurately, and the changes shown with disease will be of interest to the less specialised clinician. N. R. GALLOWAY

Radiology of the Orbit. By GLYN A. S. LLOYD. 1975. Pp. 216, figs., refs. Saunders, London (£10)

This book represents one volume in a series on diagnostic radiology. It is a tribute to the author, who has compiled a unique experience in this specialised field as consultant radiologist to Moorfields Eye Hospital and the Royal National Throat, Nose, and Ear Hospitals in London. The material is largely from his personal files and includes a lifetime of experience in the diagnosis of orbital lesions.

The early chapters describe the methods of investigating the orbit by plain x-rays, tomography, contrast techniques, computerised scanning, and various forms of ultrasound. There follow chapters on vascular anomalies in the orbit, unilateral proptosis, tumours, and pseudotumours. A useful chapter is included on the paranasal sinus, and of particular interest to clinical opthalmologists are the chapters on dacryocystography and localisation of intraocular foreign bodies.

The book is well produced, with illustrations of exceptional quality and a useful bibliography. It will prove valuable to ophthalmologists as well as neuroradiologists, for whom it was largely intended. It is unfortunate that the date of publication precluded any major consideration of computerised scanning. M. D. SANDERS

New Developments in Ophthalmology. Documenta Ophthalmologica Proceedings Series, Vol. 7. Edited by A. F. DEUTMAN. 1976. Pp. 365, 244 figs, 35 tables, refs. Junk: The Hague (Dtch. Glds. 110)

This report of the symposium held to inaugurate the new eye institute of the University of Nijmegen has no particular theme except that it is concerned with new developments in ophthalmology. It must have been an excellent symposium to attend, characterised by papers from eminent contributors on a wide variety of subjects. This ensures that all ophthalmic surgeons will find something to interest them but makes it more difficult to recommend the volume to any particular group. There are several papers on detachment of the retina and related subjects, several on the investigation and treatment of retinal disorders, and individual contributions on corneal disease, vitreous surgery, cataract surgery, and the excision of choroidal melanomas. Most of the work has been published elsewhere, and specialists in any particular topic will probably find little new, but the general ophthalmologist will find useful views on several important subjects. Few people will read every word, but most surgeons will find something of real value.

A. STANWORTH

Notes

Ophthalmic Microsurgery

A course in ophthalmic microsurgery will be held at Moorfields Eye Hospital (City Road branch) on 5–7 October. It will be conducted by the Department of Clinical Ophthalmology and is a practical course concerning the application of the operating microscope to common ophthalmic surgical procedures. Applications are invited from consultants, senior registrars, or those overseas holding equivalent positions. Previous experience with the operating microscope is not necessary, but ophthalmic surgical experience is essential.

The closing date for applications is 2 September. Application forms and further details may be obtained from Mrs J. F. Field, Microsurgical Course Secretary, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD.

Conference on Atherosclerosis

Milan, 9–11 November 1977

An international conference on atherosclerosis, sponsored by the European Group for the Study of Atherosclerosis and the Italian Society for Atherosclerosis Research and organised by the Lorenzini Foundation of Milan, will take place in Milan on 9–11 November 1977. There will be the following sessions: (1) atherosclerosis and the heart; (2) atherosclerosis and the brain; (3) atherosclerosis and the peripheral circulation, and round tables on primary and secondary prevention, new analogues of clofibrate, lipoprotein metabolism, platelet antiaggregants, dietary prevention of atherosclerosis, mucopolysaccharides, phospholipids, and new antiatherosclerotic agents. Requests for information should be sent to Fondazione G. Lorenzini, Via Montenapoleone 23, Milano, Italy.

International Workshop in Neuro-ophthalmology

Iowa City, 10–12 November

The topics at this meeting, sponsored by the Department of Ophthalmology, University of Iowa, will be: (1) Perimetry in neuro-ophthalmology (Frisén, Sweden). (2) Pupils (Thompson, Iowa City). (3) Disc swelling (Glaser, Miami). (4) Visual evoked responses (Glaser, Miami). (5) Cerebellar control of eye movements (Daroff, Miami). (6) CT scanning in neuro-ophthalmology (Sanders, London). Further information from Dr H. Stanley Thompson, Department of Ophthalmology, University of Iowa, Iowa City, Iowa 52242, USA.

United Kingdom Intraocular Implant Society

This society has recently been formed under the presidency of Mr Neil Dallas, of Bristol. The function of the society is the cultivation and promotion of intraocular implantation and consideration of matters of policy relating to this discipline. Applications for membership should be addressed to the Honorary Secretary, Mr John Pearce, 2 Windsor Street, Bromsgrove, Worcestershire B60 2BG.

European Contact Lens Society

Perpignan, 11 to 13 November

The European Contact Lens Society of Ophthalmologists Inc is sponsoring an international congress at which the subject for discussion will be 'Physiopathology—Visual Functions and Contact Lenses'. Interested ophthalmologists are welcome. Details from Dr B. Lecaillon-Thibon, BP 3019, 66000 Perpignan, France.

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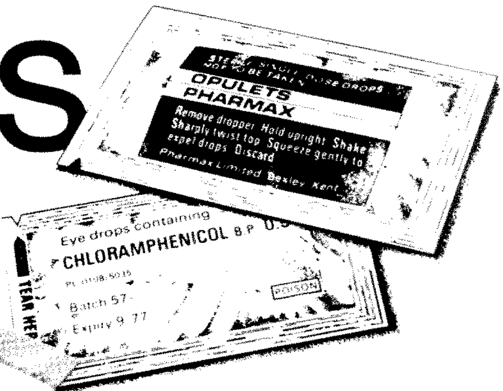
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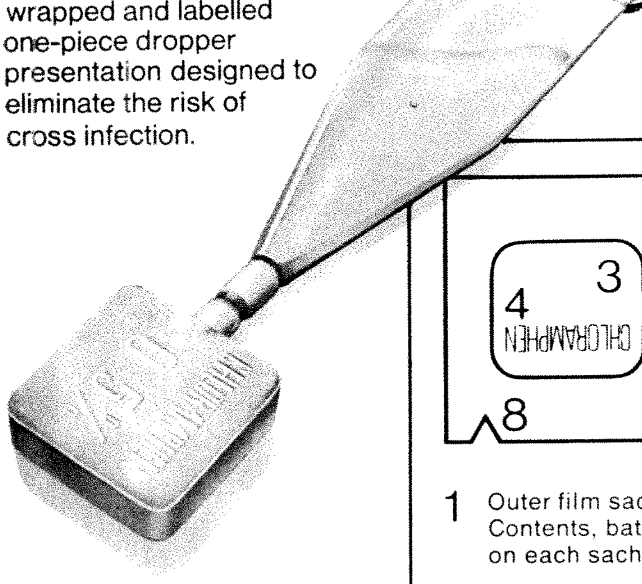

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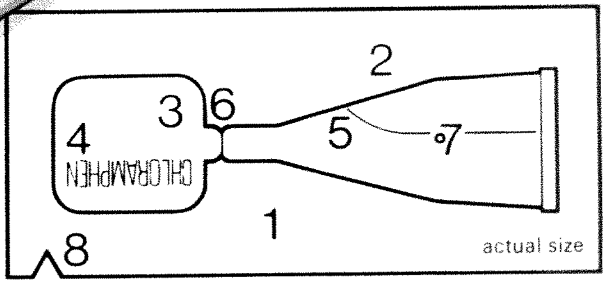

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The International Society of Geographical Ophthalmology will hold its next meeting in Cagliari Sardinia under the Chairmanship of Professor Orzalesi. Papers are invited for presentation with an emphasis on the geographic nature and distribution of the various ocular manifestations. The papers may be presented either in the Symposia or Workshops.

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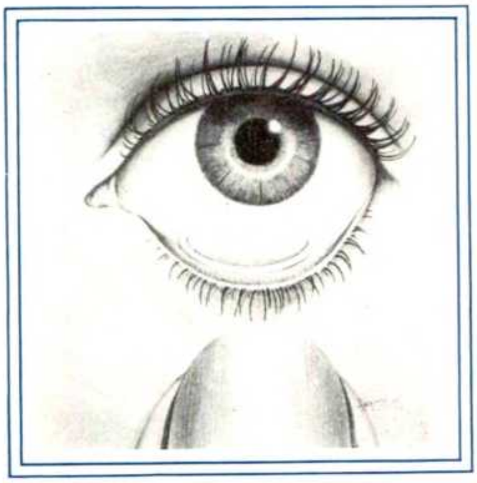

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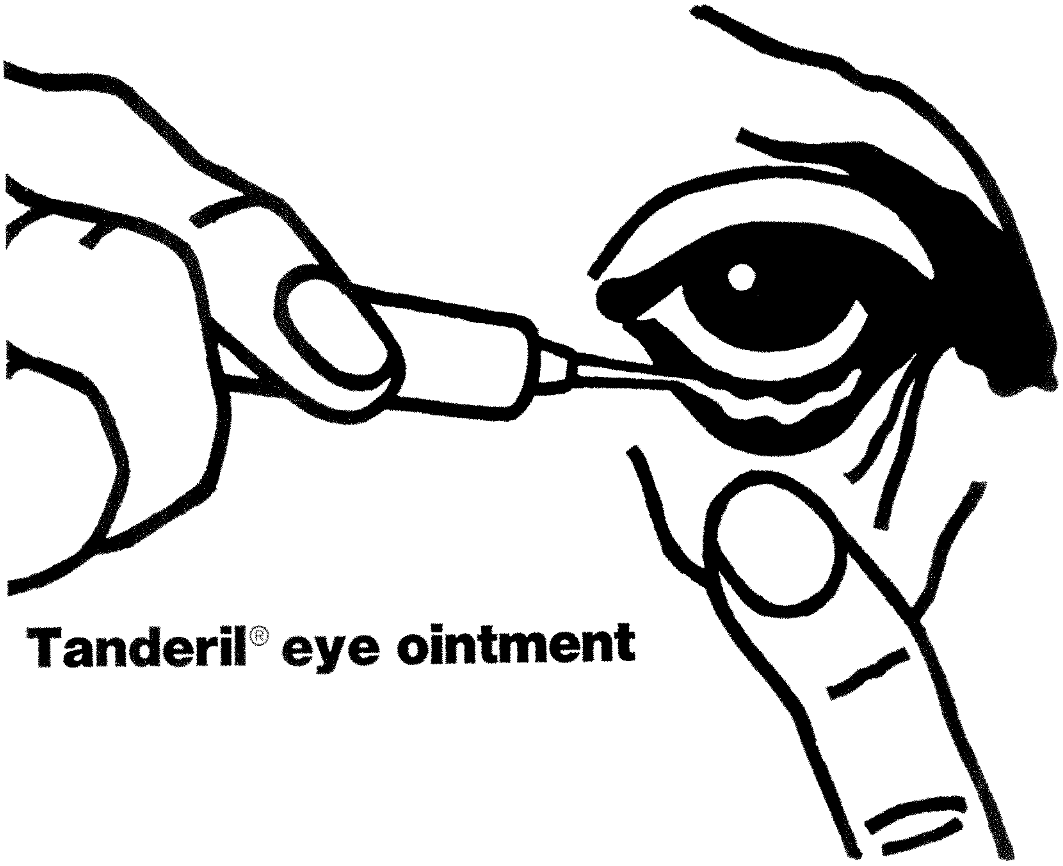

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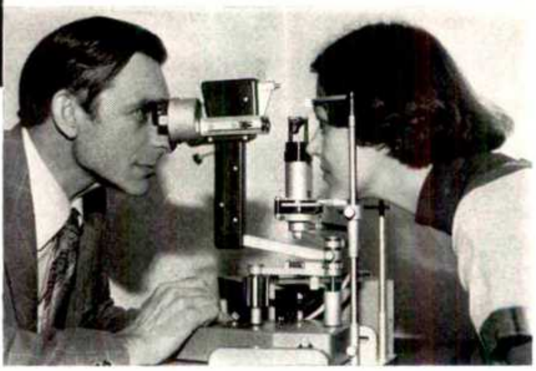

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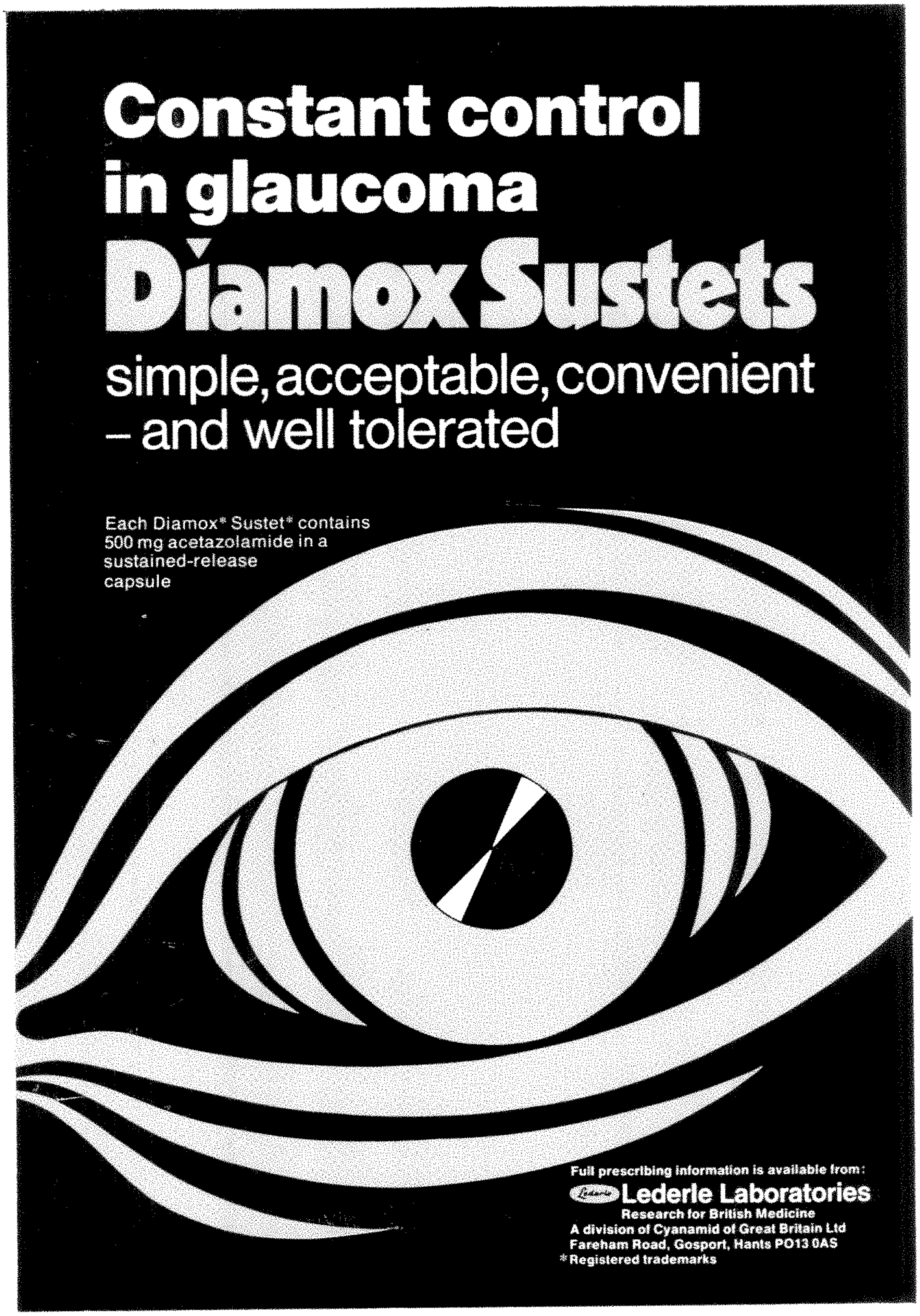

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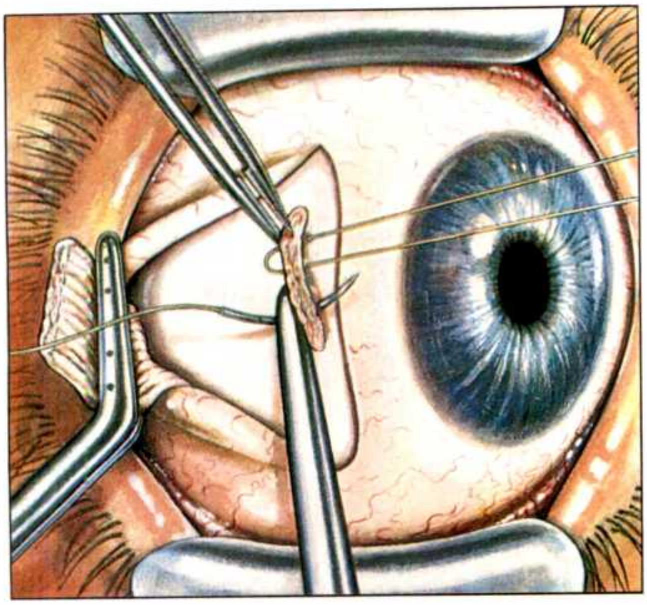

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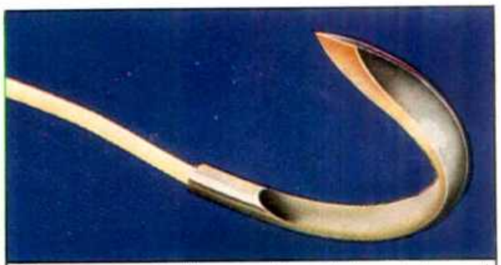

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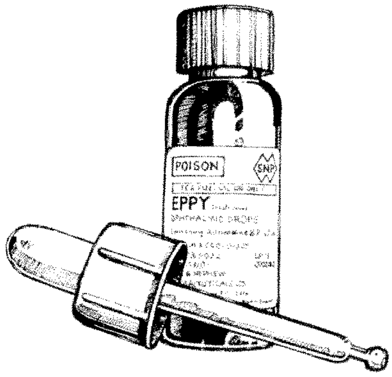

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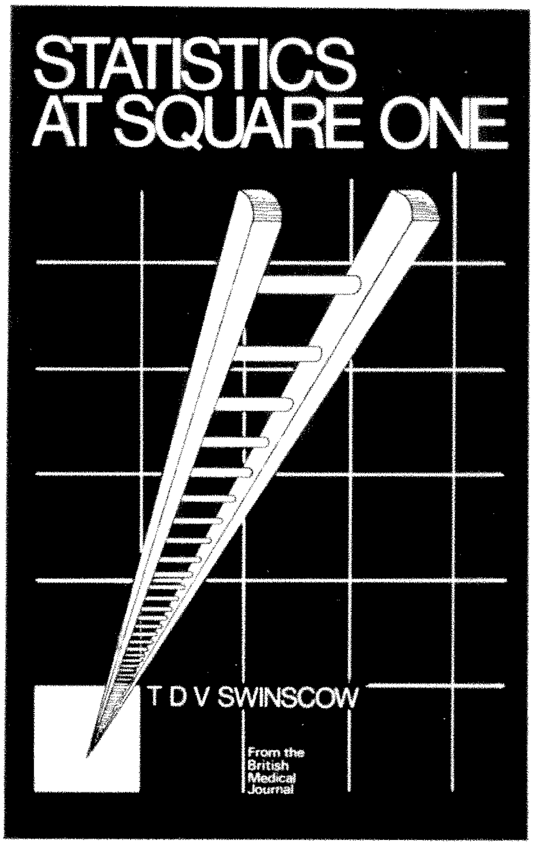

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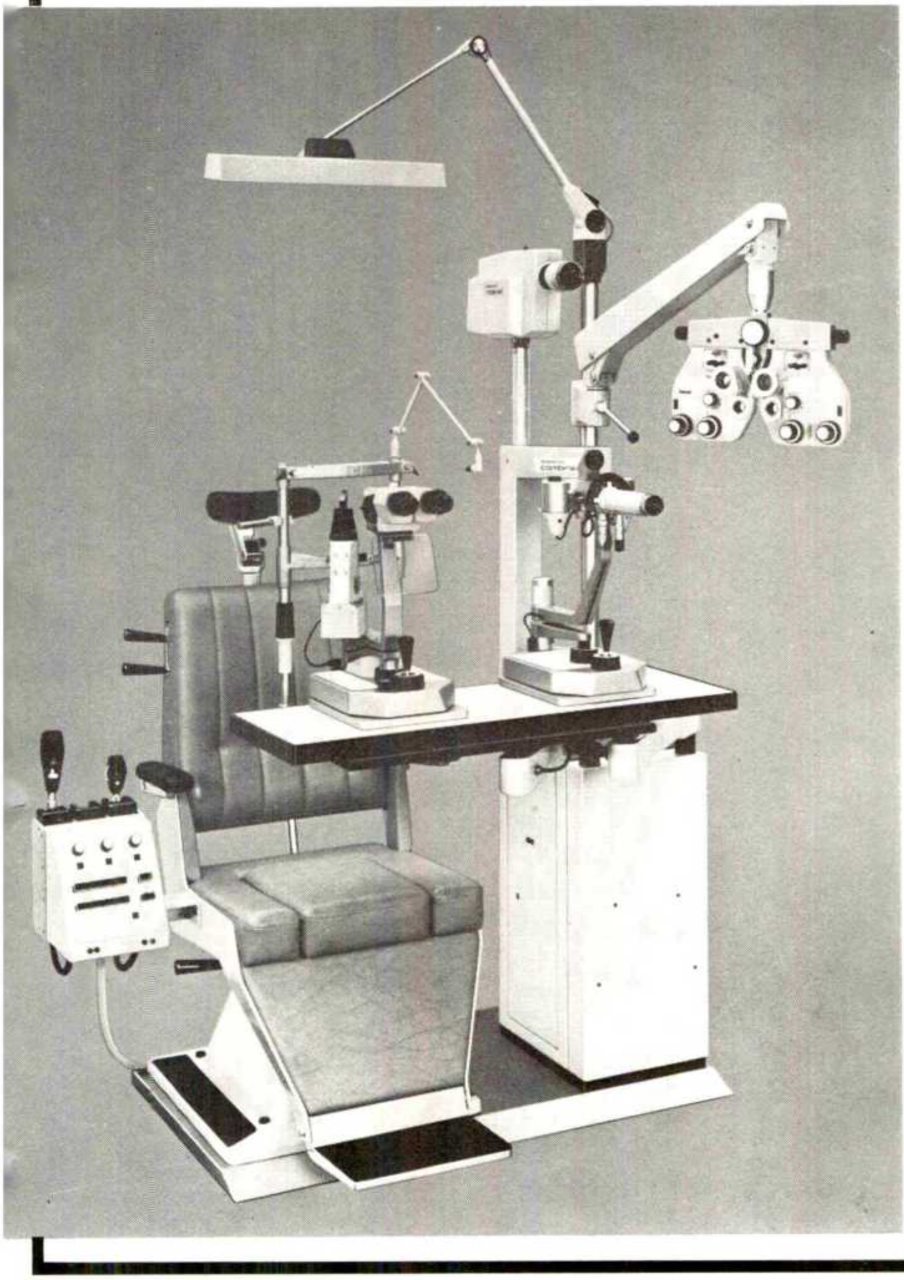

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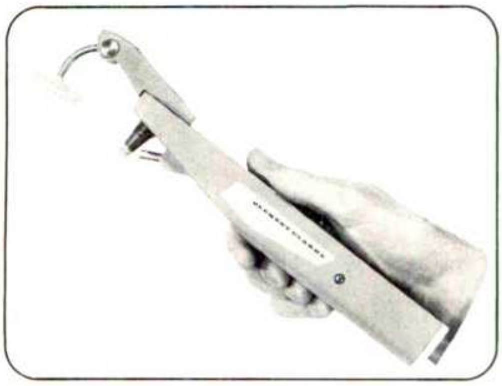

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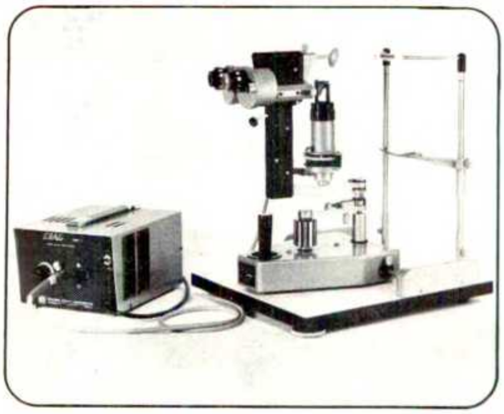

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Rapid B-scanning of the vitreous

DAVID McLEOD, MARIE RESTORI, AND JOHN E. WRIGHT
From the Vitreous Clinic, Moorfields Eye Hospital, and the Ultrasonic Department, Department of Clinical Ophthalmology, Institute of Ophthalmology, London

SUMMARY Ultrasonic examination is an essential investigation in most patients awaiting vitrectomy. Rapid B-scanning of the vitreous is described utilising a new system capable of high resolution and good tonal quality. Several patterns of haemorrhagic invasion of the vitreous cavity are illustrated, together with detachment, collapse, and retraction of the vitreous gel.

Diagnostic ultrasound has been used for many years for the investigation of ocular and orbital diseases (Oksala, 1963; Baum, 1964; Purnell, 1966; Ossoinig, 1972; Coleman, 1972; Bronson, 1972). Examination methods currently available include A-, B-, C-, and M-scanning and ultrasonic holography. Apparatus capable of ophthalmic A-, B-, and C-scanning and holography was designed by Aldridge *et al.* (1974) and has been on clinical trial at Moorfields Eye Hospital for the past three years. A report of its use in the investigation of orbital lesions is to be published shortly (Restori and Wright, 1977). This paper presents our experience of real-time B-scanning of the vitreous cavity, particularly in patients being considered for vitrectomy.

Material and methods

EQUIPMENT

A 10-MHz focused transducer is mechanically scanned in rectilinear fashion, each 4-cm sweep constituting a B-scan section. Each sweep takes approximately 140 milliseconds to complete, thereby permitting fast, almost real-time imaging of the globe. A remote button (sited near the display oscilloscope) controls the level of the B-scan section, which can be varied over a distance of 4 cm. This level is displayed on a millimetre scale and can be conveniently compared with the position of the central B-scan section, that is, the section with the strongest corneal echoes. B-scans may be taken in horizontal, saggital, and oblique planes, and the 4-cm-square scanning aperture can be completely investigated in a few seconds. Variable system controls include gain, transmission pulse duration, scanning speed, and a swept gain facility to compensate for sound attenuation in the globe and orbit.

The system is capable of good resolution and is remarkably free of artefacts. The scanning mechanism has been built to a high standard of rigidity and precision, and the instantaneous position of the transducer is transferred to the display tube with minimum error. These are design criteria for holographic imaging and undoubtedly contribute to the quality of the B-scan display.

Adequate sensitivity and accurate echo registration allow weak echoes to be detected and displayed. The dynamic range of the system is 40 dB, and an amplifier to compress this 40 dB into the 20 dB dynamic range of an oscilloscope would improve the grey scale appearance of the B-scan display.

A time-gate has proved useful in selecting echoes for amplitude quantitation from any B-scan section. The A-scan suffers no signal processing except optional rectification and envelope detection. Polaroid Landpack film (type 107C) is used to obtain a permanent record of both A- and B-scan displays; however, many of the grey tones are lost to Polaroid film and essential dynamic information is difficult to capture on still photographs.

TECHNIQUE

The eye to be investigated is anaesthetised with oxybuprocaine HCl (Benoxinate) drops and the eyelids are retracted with a Barraquer speculum. The patient lies supine on a movable couch, and the transducer is coupled to the eye by means of a Steridrape bath (Purnell, 1966) containing Ringer's solution at 36°C. The eye is positioned to lie in the centre of the 4-cm-square scanning aperture, and is

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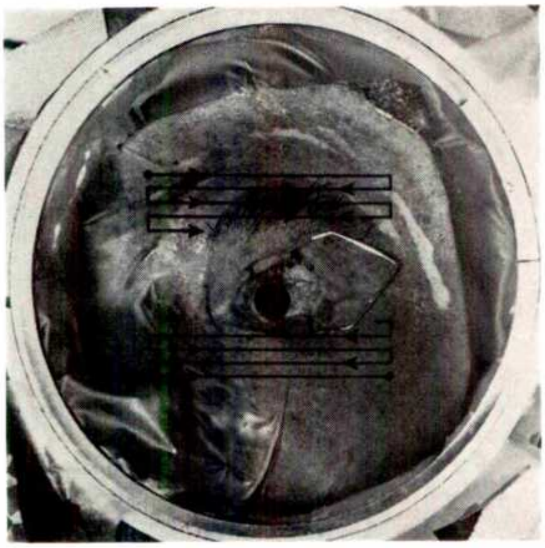

Fig. 1 *Rectilinear scanning in horizontal plane*

scanned transversely at 1-mm intervals, initially with the patient looking straight ahead (Fig. 1). Further scanning is then carried out during lateral and vertical deviations of the patient's gaze, thereby increasing the amount of data obtained from the equatorial regions of the eye. If necessary, saggital scanning is also performed, for example, to localise radiolucent intraocular foreign bodies in 3 mutually perpendicular planes.

In dynamic studies the direction of gaze is changed suddenly, and after-movements of the echoes are observed for several seconds.

CLINICAL CORRELATION

Ultrasonic findings have been correlated with ophthalmoscopic and biomicroscopic appearances wherever possible, for example, during vitrectomy performed or witnessed by one of the authors (D. McL.).

Results

The vitreous cavity is the space behind the posterior lens capsule and zonule and internal to the inner limiting lamina of the ciliary epithelium, retina, and optic disc. This space is normally occupied by the vitreous body, a relatively homogeneous aqueous gel, so the vitreous cavity is normally spheroidal on serial B-scanning (apart from the lenticular indentation anteriorly) and is acoustically 'empty'.

Acoustic changes in the vitreous have been classified as follows:

I. ABNORMAL CONTENTS OF THE VITREOUS CAVITY

The presence of echoes within the vitreous cavity indicated:

(1) persistence (or hyperplastic persistence) of primary vitreous structures (Fig. 2*a*);
(2) change in the physicochemical structure of the vitreous body, for example, senile or myopic degeneration; or
(3) invasion or infiltration of the vitreous by substances, cells, or other particles normally foreign to this cavity (Fig. 2*b*).

II. CHANGE IN THE VOLUME AND SHAPE OF THE VITREOUS CAVITY

The volume of the vitreous cavity was increased in myopic and buphthalmic eyes, an asymmetrical enlargement being interpreted as a staphyloma. Likewise in aphakia the vitreous cavity incorporated the posterior chamber, communicating with the anterior chamber via the pupil.

The volume of the vitreous cavity was reduced in microphthalmic eyes and in phthisis bulbi (where choroidal thickening compounded the effect of scleral shrinkage on vitreous volume). An asymmetrical reduction in volume typically resulted from surgical explants and orbital tumours, and also from detachments and tumours of the retina and choroid (Fig. 2*c*).

III. CHANGE IN THE VOLUME AND SHAPE OF THE VITREOUS BODY

The vitreous body commonly occupied rather less than the total volume of the vitreous cavity, separating from its surroundings anterior and/or posterior to its firm annular attachment to the pars plana and peripheral retina (the 'vitreous base'). The vitreous cavity thus became divided into compartments—that is, the vitreous gel (formed vitreous) and prehyaloid or retrohyaloid spaces (fluid vitreous)—and the shapes of these compartments were mutually interdependent. In many cases abnormal vitreoretinal adhesions precluded complete posterior detachment of the vitreous from the retina (Fig. 2*d*).

B-scanning of the vitreous cavity was most commonly performed as part of the work-up of potential cases for vitrectomy, and ultrasonic evaluation in these patients was particularly directed towards:

(A) localising and identifying material which had invaded the vitreous cavity;
(B) determining the presence of compartments within the vitreous cavity; and
(C) defining the borders of the vitreous cavity, in particular detecting the presence of a retinal detachment.

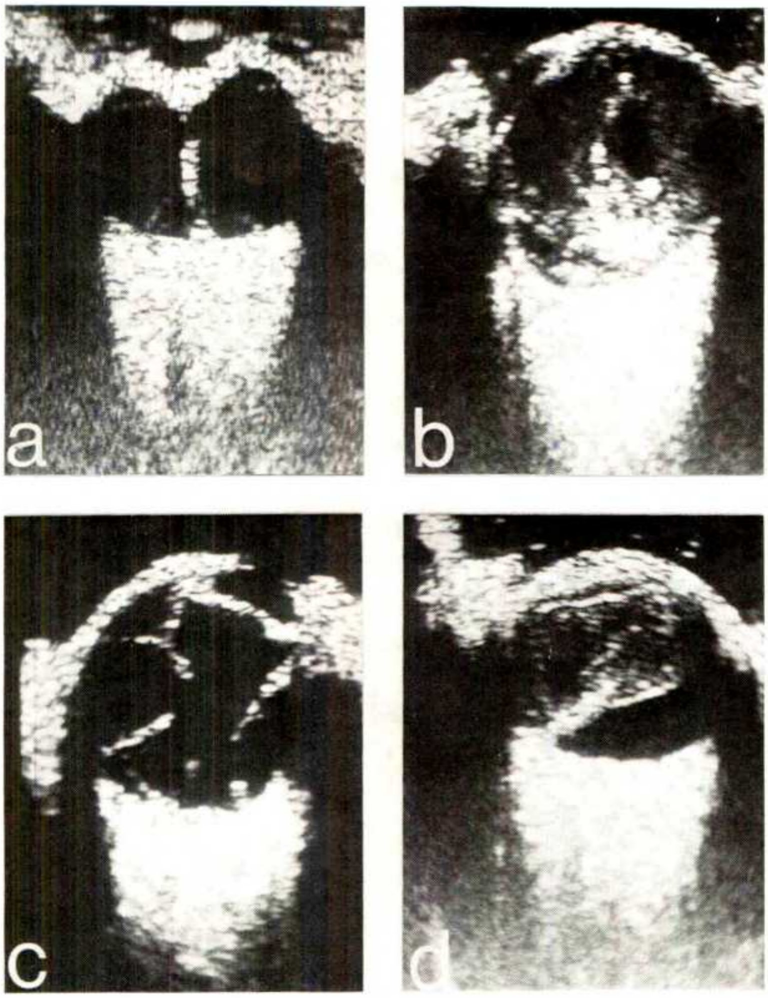

Fig. 2 *Classification of vitreous disorders*

(a) *Left eye: persistent hyperplastic primary vitreous*

(b) *Left eye, deviated nasally: invasion of vitreous by haemorrhage, densest posteriorly*

(c) *Right eye, deviated nasally: ciliochoroidal detachment tethering at scleral spur and vortex ampulla*

(d) *Left eye: dense intragel haemorrhage; foreign body track and vitreoretinal adhesion nasally; thickened anterior and posterior hyaloid membranes*

(*A*) INVASION OF THE VITREOUS (Fig. 3)
Extraneous intravitreal material gave rise to either localised or more generalised echoes from the vitreous cavity:

(1) *Localised echoes.* Inflammatory cells forming a vitreous abscess or granuloma produced a collection of medium-amplitude echoes, as did haemorrhages into relatively solid vitreous gel. Clotted blood was often confined within vitreous 'tracts' or other intragel compartments (Fig. 3*a*), and in many cases the site of bleeding could be located by serial scanning of the globe (Fig. 3*b*). Stronger and more discrete echoes arose from glial or fibrovascular tissue proliferating as a sequel to haemorrhage in the gel, for example, along the track of a perforating foreign body (Fig. 2*d*). Similarly, sheets of glial or fibrovascular tissue arranged as epiretinal membranes gave rise to high-amplitude echoes which tended to flatten the concavity of the vitreoretinal interface (Fig. 3*b*).

Collections of high-amplitude echoes also resulted from intravitreal foreign bodies or a posteriorly dislocated lens.

(2) *Dispersed echoes.* Uveitis and vitreous haemorrhage often resulted in low-amplitude echoes disseminated within the vitreous cavity (Fig. 3*c*), a picture also seen occasionally in degenerative syneresis. In general, inflammatory cells could not be distinguished ultrasonically from red blood cells, and the amount of acoustic change was less than that expected from the degree of opacification of the media to light.

Dispersed high-amplitude echoes were typical of asteroid hyalitis.

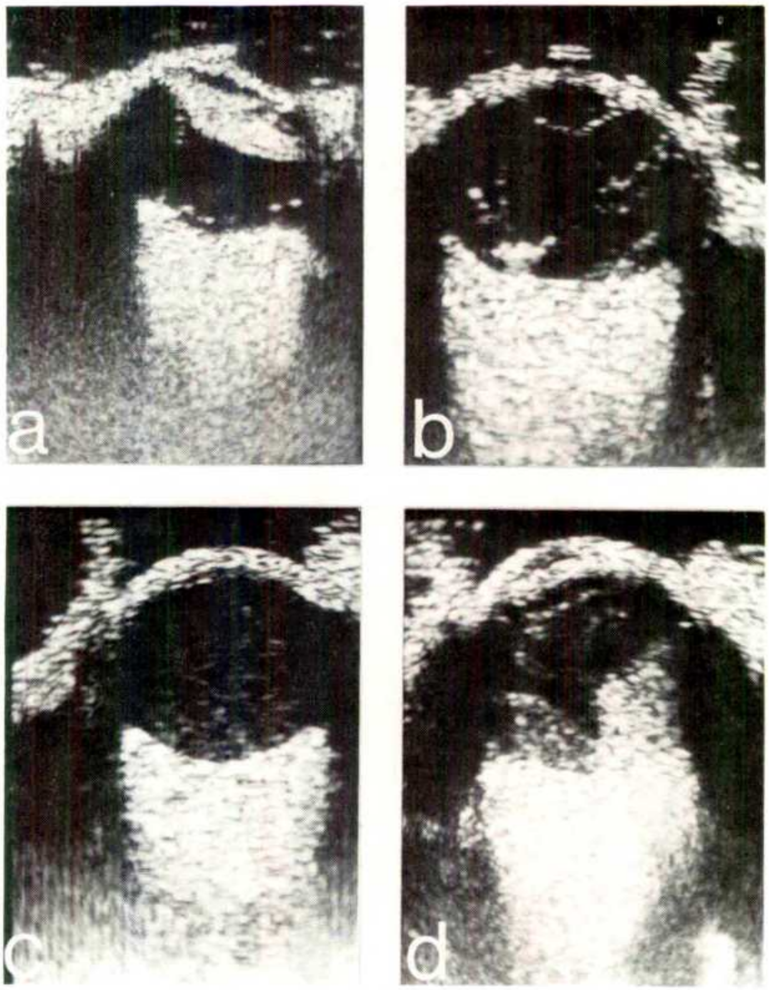

Fig. 3 *Invasion of the vitreous*

(a) *Left eye, deviated temporally; dense haemorrhage in anterior gel; fine vitreous membrane tethering posteriorly*

(b) *Left eye: haemorrhage from fibrovascular proliferations; epiretinal membrane flattens concavity of vitreoretinal interface posteriorly*

(c) *Right eye: dispersed echoes in vitreous gel.*

(d) *Right eye, deviated temporally: diffuse echoes from blood in retrohyaloid space extending into the central gel*

(3) *Diffuse echoes.* Invasion of the vitreous cavity by inflammatory or red blood cells sometimes gave rise to diffuse low-amplitude echoes by scattering of sound, producing a relatively uniform echo density (Fig. 3*d*).

(*B*) POSTERIOR VITREOUS DETACHMENT (Figs. 4 and 5)

Separation of the vitreous body from the retina was often demonstrable, especially in patients with an associated invasion or infiltration of the vitreous cavity. There were two basic acoustic patterns indicative of vitreous detachment:

(1) *A thin sheet of echoes along the posterior hyaloid interface,* usually inserting into the retina just anterior to the equator. This pattern was typically found in those diabetic patients in whom a relatively immobile membrane spanned the posterior part of the vitreous cavity, often attached to the optic disc region by a thick rigid stalk. Echoes from the posterior hyaloid membrane were of lower amplitude and more discrete than the echoes from fibrovascular tissue on the posterior aspect of the hyaloid membrane (Fig. 4*a*).

In senile and myopic posterior vitreous detachment irregular low-amplitude echoes arose from the mobile posterior hyaloid, while vitreous retraction—that is, gross anterior contraction and immobilisation of the gel (Fig. 4*b*)—was usually associated with high-amplitude echoes from a taut posterior hyaloid membrane.

(2) *Localisation of diffuse or dispersed echoes to one or other vitreous compartment,* the other compartment being clear or containing a different echo

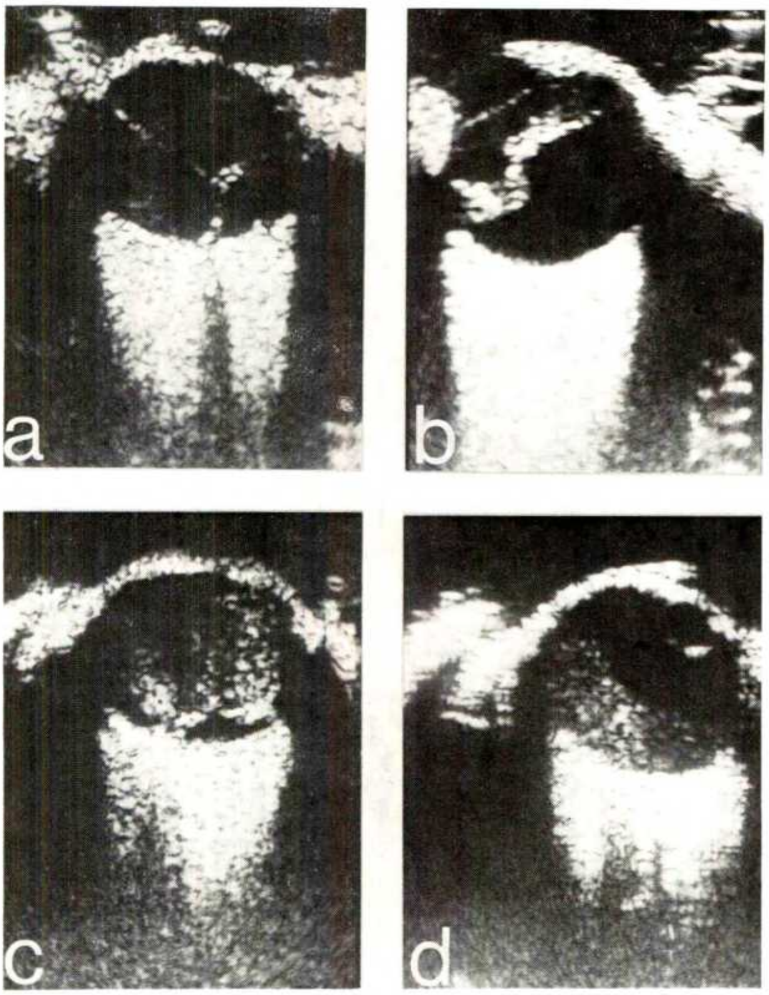

Fig. 4 *Posterior vitreous detachment*

(a) *Right eye: irregular echoes from posterior hyaloid membrane; fibrovascular stalk arising from disc*

(b) *Left eye, deviated nasally: aniridic and aphakic; gel retraction and haemorrhage; thickened immobile anterior and posterior hyaloid membranes*

(c) *Left eye: dense intragel haemorrhage and two vitreoretinal adhesions*

(d) *Right eye, deviated nasally: diffuse echoes from blood in retrohyaloid space and clear gel*

density (Fig. 4*c* and *d*). Thus, intragel echoes were often bounded by a clear retrohyaloid space (Fig. 4*c*), or an acoustically clear gel was delineated by diffuse echoes from the retrohyaloid space (Fig. 4*d*). In some patients the vitreous gel was immobile (Fig. 4*d*) or moved without significant change in contour, indicating gel contraction without collapse. In other cases, however, jerky after-movements of the posterior hyaloid interface characterised gel mobility. Extreme mobility of the gel was seen in myopes with a bleeding retinal tear and in most cases of vitreous haemorrhage due to retinal branch vein occlusion; such a pattern signified posterior vitreous detachment with gel collapse (Fig. 5*a* and *b*).

Echoes arising from one or other vitreous compartment did not necessarily fill that compartment. For example, a gradual settling of a retrohyaloid bleed over the posterior pole sometimes occurred during the course of ultrasonic examination in the supine position (Fig. 5*c*). More commonly an apparent 'compaction' of intragel echoes along the posterior hyaloid interface resulted in a thick membrane with a discrete, smooth, posterior surface (Fig. 5*d*), and at vitrectomy a dense non-fibrotic 'ochre' membrane was found. Such membranes were characteristically mobile, though the thicker the membrane the more restrained the gel after-movements became. No ultrasonic evidence of compaction of blood from the retrohyaloid space on to the *posterior* aspect of the hyaloid interface has been observed to date.

The degree of contraction of gel volume, the extent of residual vitreoretinal adhesion, and the mobility of the gel were all variable. In eyes with a

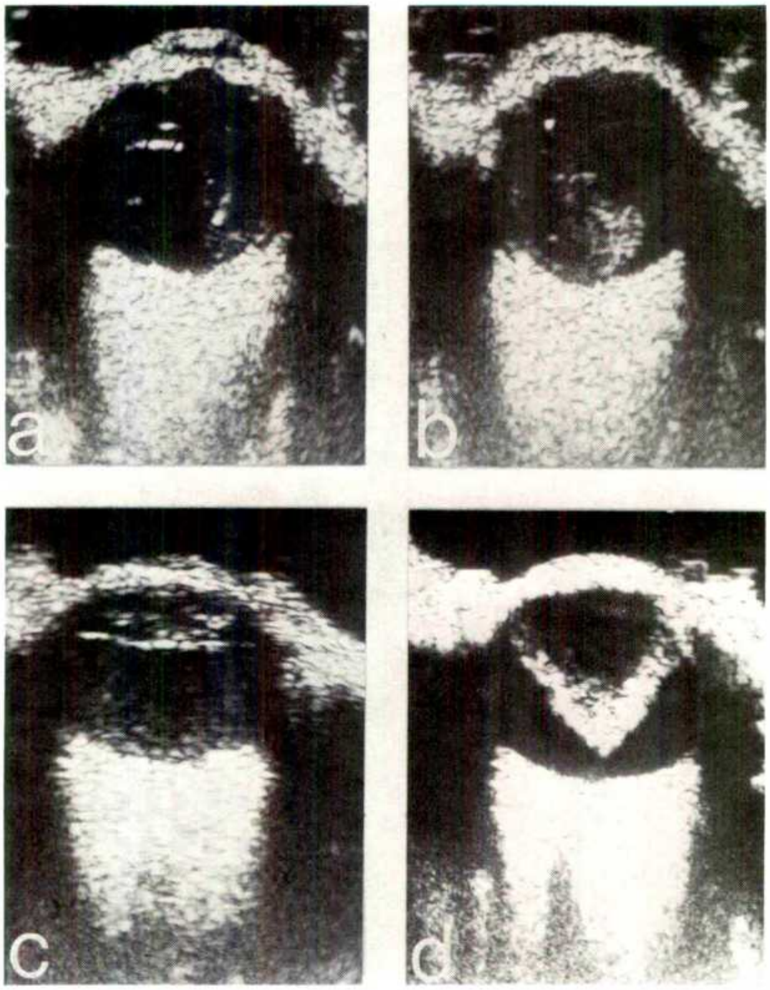

Fig. 5 *Posterior vitreous detachment*

(a) *Left eye, not deviated: intragel haemorrhage temporally; clear retrohyaloid space nasally.*

(b) *Same eye as* 5(a), *deviated nasally: intragel haemorrhage now on nasal side; clear retrohyaloid space temporally*

(c) *Left eye: dense haemorrhage in retracted gel and thickened posterior hyaloid membrane; retrohyaloid haemorrhage sediments on to posterior retina*

(d) *Left eye: dense intragel haemorrhage showing 'compaction' posteriorly and tethering at the macula—an ochre membrane*

minimally contracted mobile vitreous body the gel tended to settle against the retina under the influence of gravity in the supine position. In such cases dynamic testing was necessary in order to separate the vitreous and retina and to identify points of true vitreoretinal adhesion, which might be extremely tenuous, for example, after neovascularisation due to retinal branch vein occlusion. Tumours or retinal detachments underlying the haemorrhage could also be discovered in this way.

(*C*) DETACHMENT OF THE RETINA (Fig. 6)
Detached retina produced a regular continuous sheet of high-amplitude echoes which encroached on the vitreous cavity. When the detachment was extensive and bullous, the membrane typically showed undulating after-movements on dynamic testing and was usually characterised by attachments at the ora serrata and optic nerve head (Fig. 6*a* and *b*). The site of communication between the vitreous cavity and the subretinal space in eyes with rhegmatogenous retinal detachment was detected only in cases of giant retinal tear or dialysis (Fig. 6*c* and *d*). The subretinal space was generally clear, though subretinal haemorrhage or tumour was occasionally present.

In many eyes there were also acoustic signs of invasion of the vitreous cavity by red blood cells or pigment cells (Fig. 6*b*) or evidence of posterior vitreous detachment (Fig. 6*a* and *d*). In traction retinal detachments a taut posterior hyaloid membrane typically inserted into the height of an immobile elevation of the retina. Alternatively, if the detachment resulted from transgel traction-band

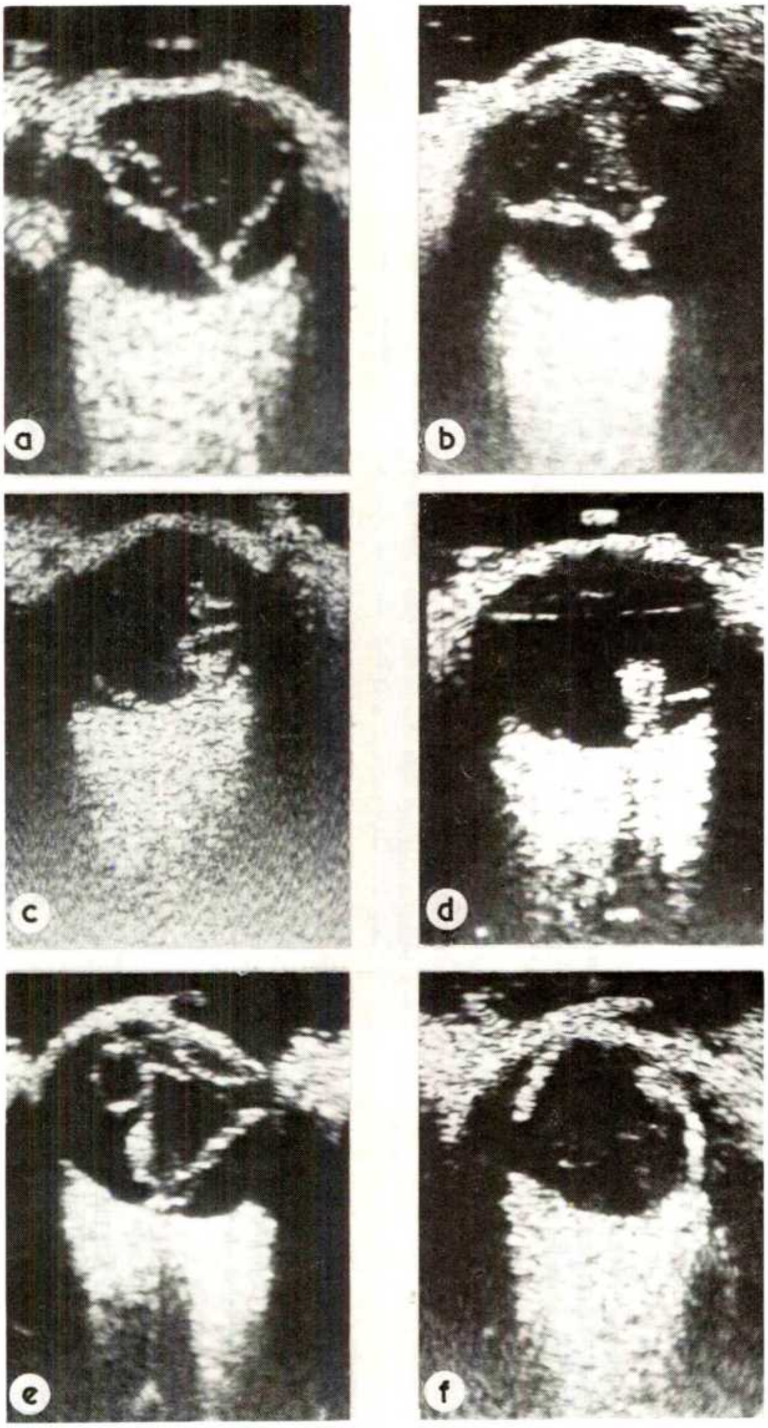

Fig. 6 *Detachment of the retina*

(a) *Left eye: detached retina tethers at the disc and ora serrata; mobile posterior hyaloid membrane*

(b) *Left eye, deviated nasally: totally detached retina; pigment invasion of gel.*

(c) *Left eye: giant traumatic retinal dialysis; gel attached to folded temporal retina and pars plana; shallow nasal retinal detachment*

(d) *Right eye: giant retinal tear; folded-over temporal retina at disc; detachment nasally; gross gel retraction and taut posterior hyaloid membrane*

(e) *Right eye, deviated nasally: vitreous retraction; epiretinal fibrosis; 'morning glory' retinal detachment; retinal cyst*

(f) *Left eye: retinal detachment secondary to anterior vitreous traction; pars plana is detached but posterior retina is flat; posterior vitreous detachment (mobile on dynamic testing)* formation or from severe contraction of epiretinal membranes, the posterior hyaloid could be quite mobile. In eyes with massive preretinal retraction fibrous proliferation along the posterior hyaloid interface typically resulted in a taut, immobile sheet of high-amplitude echoes across the vitreous cavity (Fig. 6*d* and *e*). Associated epiretinal membrane formation was suggested by retinal immobility together with thickening and shortening of the retina (Fig. 6*e*), while in some cases the epiretinal membranes were discernible between the retinal folds.

Detached retina was usually readily differentiated from a vitreous membrane, which generally gave rise to an irregular sheet of echoes of lower amplitude and greater mobility than retina with discrete or absent attachments posteriorly (Fig. 4*a*). Similarly, although elevation of the neuroepithelium sometimes extended anterior to the ora serrata in traction retinal detachments (Fig. 6*f*), there was seldom any real source of confusion with a choroidal detachment (Fig. 2*c*). However, some difficulty was experienced in differentiating a very shallow traction detachment of the posterior retina from epiretinal fibrous tissue or a taut fibrous minimally detached posterior hyaloid membrane. Similarly, a dense posterior hyaloid membrane tethered by a wide adhesion to the optic nerve-head sometimes simulated a total retinal detachment. In such cases particular attention was paid to dynamic and tonal features such as signs of compaction.

Discussion

Recent advances in vitreous surgery have provided an added impetus to improving the ultrasonic assessment of the vitreous cavity. The B-scan method, which provides a cross-sectional image of the interior of the globe, is undoubtedly the most useful technique in the investigation of patients awaiting vitrectomy. Standardised A-scan systems (such as the Kretztechnik 7200 mA) provide quantitative data on intraocular echoes such that detached retina can be differentiated from a vitreous membrane in many cases (Ossoinig, 1972). However, vital dynamic and topographic characteristics of vitreous pathology are much more readily determined by rapid B-scanning, and we use the A-scan to provide supplementary information in relatively few cases.

Although contact scanning offers certain advantages in respect of preparation time and patient acceptability, water-bath coupling eliminates problems associated with working in the near-field of the transducer and also permits echoes from the anterior segment to be displayed. Furthermore, a wide linear transducer excursion allows landmarks on both sides of the globe to be represented simultaneously, providing a good field of view of both anterior and posterior structures with minimal geometrical distortion of the display. One potential problem of linear scanning, of course, is the inability to display flat structures which are not at approximately normal incidence to the sound beam. This can be overcome by examining the eye in different directions of gaze, so structures become more favourably orientated to the beam. Thus, compound scanning capability has been found to offer no real advantage in the assessment of the vitreous cavity.

The Moorfields system combines several features essential for complete ultrasonic assessment of the vitreous cavity, in particular real-time imaging and good tonal quality. Furthermore, resolution is maintained despite spontaneous eye movements and during dynamic testing. In our hands the limited real-time scanning facility and lack of tonal quality of the Sonometrics Ophthalmoscan are considerable drawbacks to adequate previtrectomy assessment. The possibility of operator-induced errors (such as overwriting) from a manual scanning system, unless used in conjunction with a scan converter, is a further disadvantage.

With the Moorfields B-scan system dynamic vitreoretinal interrelationships can be graphically illustrated in a variety of conditions. Thus the independent mobility of the vitreous gel and the posterior edge of giant equatorial retinal tears may be contrasted with the attachment of vitreous gel to detached pars plana and peripheral retina in giant traumatic retinal dialyses. In other rhegmatogenous detachments the process of vitreous retraction can be followed, the posterior hyaloid changing from a thin mobile interface to a taut fibrous membrane (designated a 'cyclitic' membrane in some of the ultrasonic literature). When associated with a funnelled 'morning glory' retinal detachment, echoes from this membrane contribute to the so-called 'triangle sign' (Fuller, 1976), which has been considered to indicate inoperability of the retinal detachment by vitrectomy and membranectomy. Nevertheless such detachments can sometimes be re-attached by silicone oil injection into the retrohyaloid space. We believe gross shortening and fixed folding of the retina are the best guides to inoperability.

Finally, repeated B-scanning has also allowed the development of posterior vitreous separation to be followed in cases of haemorrhagic invasion of the gel. Such patients often complain of a further reduction in vision some time after initial visual loss, and dynamic testing suggests that a centrifugation or compaction of intragel particles has occurred owing to increased gel movement following vitreous detachment. We hesitate to use the term 'organised vitreous membrane' to describe such an arrangement of haemorrhage, since 'organisation' implies massive fibrovascular invasion and immobilisation of a long-standing haemorrhage, none of which features characterises ochre membranes.

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Retinal mobility and retinal detachment surgery

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SUMMARY A series of 200 consecutive retinal detachments was examined prospectively to consider the physical sign of mobility of the detached retina.

Retinal mobility was found to be absent in 28 cases, and this immobility is caused by periretinal membrane formation. The importance of retinal mobility when considering the case for non-drainage retinal surgery has been examined with particular emphasis on the tear/buckle relationship at the end of the operation.

It was found that there was an excellent prognosis (92% success rate) for cases in which the retina was found to be mobile in the vicinity of the retinal tear, and a high proportion of these cases (71%) can be successfully treated with a non-drainage operation.

It has been stated that the assessment of the mobility of the detached retina is an important factor (Scott, 1972; Chignell, 1974) when the non-drainage retinal detachment operation of Custodis (1953) and Lincoff *et al.* (1965) is being considered. If the retinal tear cannot be closed at the time of surgery, then the detached retina must, if the non-drainage operation is to succeed, have sufficient mobility to sink back against the buckle and close the tear. (A small increase in the height of the buckle may be expected in the immediate postoperative period owing to expansion of the sponge, as the intraocular pressure falls.) Sinking back of the detached retina takes a varying length of time from a few hours to several days, depending partly on how far it has to go. Thus the proximity of the buckle to the tear at the end of operation is an important feature; the deeper the intervening fluid, the greater must be the degree of retinal mobility if settling back is to occur. The object of the present study was to report a prospective series of retinal detachment cases to assess preoperative retinal mobility and the influence it has on the decision whether a non-drainage operation can be performed.

Retinal mobility

Two main factors effect the mobility of the detached retina. The first is the depth of subretinal fluid. If the subretinal fluid is shallow, there is very little scope for actual movement of the detached retina, which, in fact, may then appear to be relatively immobile. This situation is rarely of clinical significance, as in the presence of minimal fluid the retinal hole can easily be closed at the time of surgery with a non-drainage operation. The second circumstance in which retinal mobility is reduced is when the detached retina is converted into a more rigid structure by the presence of fibrotic retinal membranes, membranes which may form at either surface of the detached retina (Machemer and Laqua, 1975; Laqua and Machemer, 1975). The denser the membrane, the greater will be its immobilising effect. It is the latter problem of immobility that is of particular importance to the surgeon, both preoperatively and at the time of operation, in assessing whether or not the non-drainage operation can be expected to succeed.

Materials and methods

Two hundred consecutive cases of retinal detachment admitted to the Retinal Unit of the Eye Department, St. Thomas's Hospital, London, were studied. All cases, including those that had been previously operated upon elsewhere, were included. The follow-up period has varied from 1 to 2½ years from the time of surgery.

Preoperative assessment

RETINAL MOBILITY

The retina was described as being mobile if any degree of undulating movement of the detached retina could be detected in the vicinity of the tears either on indirect ophthalmoscopy with scleral depression or on 3-mirror gonioscope examination.

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The retina was described as immobile if no such movement could be detected.

RETINAL MEMBRANES

The presence and position of periretinal membranes was assessed. Presumed and therefore early evidence of membrane formation was not included—for example, simple distortion of a retinal tear or of neighbouring retinal blood vessels, changes which usually precede the onset of the visible white membrane (Scott, 1975). Only when actual whiteness of the membrane could be detected was it included in the series. The degree of membrane formation varied considerably from small patches of preretinal membrane to end-stage massive periretinal proliferation. The membrane was considered to be immediately related to the tear if within 1 to 2 mm.

SURGICAL DETAILS

In all cases the method of surgery was similar. Thus full-thickness scleral buckles were used. Cryotherapy was applied. Silastic episcleral sponge implants were used and, for encirclements, silicone rubber bands, which in most cases were accompanied by local implants. At the time of surgery if the retinal tear could not be closed an attempt was made to produce a high buckle and to approximate the buckle to the tear as nearly as possible. The relationship of the buckle to the tear at the end of operation was described as either tear closed, a moderate depth of subretinal fluid (the tear completely separated from the buckle, the outline of which can easily be detected), or deep subretinal fluid (the outline of the buckle more difficult to detect).

REASONS FOR DRAINAGE

For the purpose of this study the reasons for drainage, noted at the time of surgery in all cases, were considered under two main headings: (1) insufficient mobility of the detached retina; and (2) when drainage was performed for reasons other than that of retinal immobility. This included a varying group—e.g., accidental drainage with a scleral suture, a poor view of the optic disc preventing visualisation of arterial pulsation, uncertain localisation of the hole, or when intravitreal injections were being used. Sometimes a case was drained for a combination of reasons, and if insufficient mobility was among them—e.g., immobile retina and poor view of the optic disc—the case was considered as being drained for insufficient mobility.

Results and discussion

In the 200 cases performed there was an overall surgical reattachment rate of 90%; 129 cases (65%) were treated with an initial non-drainage procedure (this incidence would have been 70% but for inadvertent drainage which occurred in 9 cases). Of these 129 cases 13 needed more than one operation, in the course of which 5 further cases had subretinal fluid drained, giving an overall non-drainage rate in the cases successfully reattached of 62·2%. In the non-drainage cases local implants were successfully used in 112 cases (89%), and a combination of local and encircling buckles were used in 14 cases (11%).

RETINAL FIBROSIS

Sixty-four cases (32%) had clinical evidence of fibrosis either in the detached retina near the retinal hole or elsewhere, or both. In 40 of the 64 cases (62%) there was fibrosis in the immediate vicinity of the tear (this is probably a conservatively low figure, as in 10 cases assessment was not possible because the view of the retina in the vicinity of the tear was obscured by opacities in the media). In 24 cases (38%) the fibrosis was found only in detached retina remote from the retinal hole. This finding indicates that, although membranes favour the vicinity of tears for their formation, possibly owing to local stimuli from torn retina and also possibly from allowing easy access of pigment epithelium (with its fibrotic potential) to the vitreous cavity, this is not invariably the case.

EFFECT OF FIBROSIS ON MOBILITY

The detached retina was judged to be completely immobile in 20 out of the 40 cases where there was fibrosis in the immediate vicinity of the retinal tear. Of the 24 cases in which fibrosis was not immediately related to the retinal tear the retina near the tear was judged to be completely immobile in 8. Thus it can be seen that, although fibrosis arising in retina not immediately associated with a retinal tear does not usually immobilise the retina near the tear, it may do so. This is probably due to a splinting effect, which is likely to occur when fibrosis is central to a patch of fibrosis and situated in the same meridian.

RESULTS OF ASSESSMENT OF RETINAL MOBILITY

There were 28 cases in which the retina was considered to be completely immobile in the vicinity of the tears on the preoperative examination and 157 in which the retina was found to have a degree of mobility varying from being freely mobile to partially mobile. In the remaining 15 cases assessment was not possible owing to difficulty in observing the retina in the vicinity of the tears.

Choice of operation

IMMOBILE RETINA

A non-drainage operation was attempted in 11 of the 28 cases (Table 1). In 17 cases in this group drainage of subretinal fluid was performed in the initial operation (Table 1), and in 15 of these 17 cases this drainage was for immobility. In the 7 cases where the hole could be closed at the time of surgery (Table 2) operation was successful at the first attempt. In 4 cases there was still fluid between buckle and tear, and initial failure occurred in 2 because the retina did not settle back against the buckle, and at reoperation drainage was necessary.

In the 28 cases only 9 (32%) were successfully treated by non-drainage operation, and in 7 of these 9 it had been possible to close the tear at the time of surgery. There were 3 overall failures in this group.

MOBILE RETINA

In the 157 cases in which the retina was judged to be mobile the initial operation was a non-drainage procedure in 111 (Table 3). In the 22 non-drainage cases in which the retinal tear could be closed at the time of surgery (Table 4) all were successful with 1 operation. When there was slight intervening subretinal fluid (68 cases) 5 reoperations were necessary. In 1 of these reoperation cases drainage was performed for what was considered to be insufficient mobility of the detached retina. In the 21 cases in which deep subretinal fluid was present at the end of operation in the non-drainage group 4 reoperations were necessary, of which 1 required drainage for reasons of insufficient mobility There was 1 overall failure in this group.

Thus the total number of successful non-drainage cases in the mobile retina group was 106 (67·5%), a significant difference ($P < 0{\cdot}01$) from the successful non-drainage in the immobile retina cases. It will be seen from Table 3 that in the majority of the cases the subretinal fluid which was present was drained for reasons other than relative immboility. In only 8 (18%) was drainage initially performed for reasons of relative immobility. Although in these cases a preoperative assessment of the detached retina had indicated some degree of mobility, it was felt at the time of surgery that this was limited, and in the presence of deep subretinal fluid it was not expected that sufficient settling back of the retina in the postoperative period would occur. In the mobile retina group of 157 cases there were eventually 12 failures (an overall success rate of 92%).

Table 1 *Drainage of SRF in 28 cases of immobile retina*

Drained for immobility	15
Drained for 'other reasons'	2
Not drained	11

Table 2 *Immobile retina (28 cases). Relationship of tear to buckle at end of operation in 11 non-drained cases*

Tear closed	*Slight SRF*	*Deep SRF*
7	4	0

Table 3 *Reasons for drainage in 157 cases in which the retina was mobile*

Drained for immobility	18
Drained for 'other reasons'	28
Not drained	111

Table 4 *Mobile retina (157 cases). Relationship of tear to buckle at end of operation in 111 non-drained cases*

Closed	*Slight SRF*	*Deep SRF*
22	68	21

Conclusion

In a series of 200 consecutive cases of retinal detachment the retina was found to be completely immobile near the retinal tears (owing to retinal fibrosis) in 28 of them. Some degree of mobility at least was found in 157 cases. Retinal fibrosis was present in 64 cases (32%). In 44 cases in which fibrosis was present in the vicinity of the tear complete immobility was present in 20 cases. In spite of this a non-drainage operation may be performed, but it is necessary to close the retinal tear at the time of surgery, and two failures with non-drainage in this group emphasised this necessity. Of 24 cases in which the retinal fibrosis was not related to the tears the retina was immobile in the vicinity of the tear in 8, possibly by a splinting effect on the detached retina.

The surgical results in this series emphasise that one of the most important sequelae of retinal fibrosis is its effect on the mobility of the detached retina and the dynamic relationship the retina has with the buckle that has been raised. Thus it was found that regardless of any other feature of the detachment (e.g., size, position, multiplicity, and type of retinal hole) there was an excellent prognosis

(92% success rate) for cases in which the single physical sign of at least some retinal mobility in the vicinity of the tear is present, and a high proportion of these cases (71%) can be successfully treated with a non-drainage operation. In the cases that were drained in the mobile retina group drainage was usually performed for 'other' reasons.

In view of the improved general treatment of retinal detachment modern series are bound to contain increasing numbers of complicated cases. One of the most important preoperative problems is that of attempting to assess the mechanical effect of any retinal fibrosis that may be present. It is stressed that one of the most important features of these membranes is their effect on retinal mobility, and this physical sign is of great importance as an indicator of whether or not a successful non-drainage operation can be performed.

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Fluorescein pupillary flow in aphakics with intact and spontaneous openings of the vitreous face

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SUMMARY The passage of fluorescein dye, injected into the general circulation, from the posterior to the anterior chamber was studied in 60 selected aphakic eyes between 2 days and 4 weeks after an uneventful cataract extraction. In a group of 22 eyes with intact anterior hyaloid, fluorescein was seen to pass only through the pupillary margin, mostly within 20 seconds of the beginning of the eye injection. In 24 eyes with rents in the anterior hyaloid the dye was seen percolating only through the vitreous face openings. No fluorescein passed through the pupillary margin or the peripheral iridectomy in this group of eyes. The appearance time of the dye was delayed to about twice the normal appearance time. In 8 eyes with rents in the anterior hyaloid the dye passed only through the pupillary margin. In 4 eyes with anterior vitreous rents the fluorescein appeared through the anterior vitreous face opening.

From the analysis of the data it appears that the spontaneous breaks in the anterior vitreous face may represent a 'self-cure' of pupillary and iridectomy block by the vitreous in aphakics in a high proportion of cases. It is our impression that 3 peripheral iridectomies and a very tight closure of the wound can prevent the complication of spontaneous breaks of the vitreous face.

Rupture of the anterior hyaloid membrane after uneventful intracapsular cataract extraction is considered to be a common phenomenon both for the round pupil and sector iridectomy techniques (Jaffe, 1969).

The cause of the spontaneous rupture of the anterior hyaloid face remains speculative. Such factors as posterior vitreous separation, haemorrhagic or serous cilio-choroidal detachment, lessening of the tenacious attachment of the vitreous at its base, mechanical damage by the iris pupillary margin, activity of the patient, weakness of the anterior hyaloid, and relative pupillary block have been implicated (Jaffe, 1969). This study was undertaken to investigate whether pupillary block is related to spontaneous breaks in the anterior vitreous face. Using fluorescein dye injected into the circulation, we analysed the passage of the dye through the pupil and the iridectomy to the anterior chamber in 60 aphakic patients who underwent an uneventful cataract extraction.

Materials and methods

Sixty patients who underwent uncomplicated cataract extraction were selected for this study. The criteria for selection were their willingness to receive an intravenous fluorescein injection and their good systemic condition. Each patient was examined under the slit lamp between 2 days and 4 weeks after surgery to determine the condition of the vitreous face with regard to gaps in the anterior hyaloid face and the mode of passage of fluorescein into the anterior chamber. Table 1 gives the number of eyes with intact vitreous face and with openings in the vitreous face after cataract extraction. Thirty patients had a round pupil and 1 peripheral iridectomy. In 12 of these there were openings in the vitreous face ranging between 0·25 and 3·2 mm within the pupillary area. The other 18 had an intact anterior hyaloid.

Thirty patients had sector iridectomies. Of these, 24 had rents in the vitreous face and 6 an intact anterior vitreous. The gaps in the vitreous face in these cases varied between 0·25 and 2·5 mm in

Table 1 *Vitreous face after intracapsular cataract extraction*

	Round pupil	*Sector iridectomy*
Rents in anterior vitreous face	12	24
Intact anterior vitreous face	18	6
Total	30	30

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diameter. All the patients had normal intraocular pressures at the time of examination, but 12 of them were receiving daily doses of 0·5 to 1·0 g of acetazolamide.

To study the passage of fluorescein to the anterior chamber each patient was seated in front of the slit lamp and 2 ml of 15% fluorescein was quickly injected into the antecubital vein while the pupillary area was screened with a slit of cobalt blue light. The time between the beginning of the injection and the appearance of fluorescein in the pupillary area and iridectomy was recorded. Using a similar technique, Ray and Binkhorst (1966) found that the dye passes through the pupil to the anterior chamber in about 20 s in normal aphakic eyes, while in the presence of an aphakic pupillary block fluorescein does not appear in the anterior chamber at all or it does only after several minutes very faintly.

Results

Table 2 shows the pathway and appearance time of fluorescein in the anterior chamber in the 60 aphakic eyes included in this study. In the 22 eyes with intact vitreous face fluorescein was clearly seen percolating from the posterior to the anterior chamber through the pupillary margin. The peripheral iridectomy did not show any flow of fluorescein in this group of eyes. The appearance time of fluorescein was below 20 s in most of these eyes, the time range being between 11 and 38 s. Fig. 1 shows the passage of dye along the pupillary margin of an aphakic eye with peripheral iridectomy. In the 4 eyes with sector iridectomy in this group the dye could also be seen passing along segments of the iridectomy margins.

Table 2 *Pathway and time of fluorescein passage to the anterior chamber*

Characteristics of anterior hyaloid and pupil	*Only through pupillary margin (No. of eyes)*	*Only through vitreous rents (No. of eyes)*	*Both through pupillary margin and vitreous rents (No. of eyes)*	*Peripheral iridectomy*
Round pupil without anterior vitreous rent	18 (11 to 38 s)	—	—	—
Round pupil with anterior vitreous rent	2 (15–20)	8 (40–48 s)	2 (10*–50 s†) (12*–45 s†)	—
Sector iridectomy without anterior vitreous rent	4 (16–21 s)	—	—	—
Sector iridectomy with anterior vitreous rent	8 (12–14 s)	16 (45–52 s)	2 (10*–45 s†) (12*–52 s†)	—

*Early fluorescein passage through pupillary margin.
†Delayed fluorescein passage through anterior vitreous rent.

In 24 of the 38 eyes with openings in the anterior vitreous face fluorescein could be seen accumulating in fluid pockets within the vitreous body and flowing forward to percolate through the vitreous openings in the anterior face. No dye passage could be detected through the pupillary margin, the peripheral iridectomy, or the sector iridectomy. The appearance time of fluorescein in the anterior chamber was considerably delayed in those eyes in which passage occurred through the pupillary margin and varied between 40 and 48 s. Fig. 2 shows the passage of dye through an opening in the vitreous face. In 10 eyes of the same group with openings in the anterior hyaloid the dye passed only through the pupillary margin within 20 s of injection but not through the vitreous rents. Fig. 3 shows passage of dye along the pupillary margin but not through the vitreous face opening. In 4 eyes with vitreous face rents the passage of dye occurred through both the pupillary margin and the vitreous face openings. In these eyes there was an early passage of fluorescein through the pupillary margin at 10 to 12 s after the injection and a delayed appearance through the vitreous face gap at 45 to 52 s. Fig. 4 shows the dye percolating through both the pupillary margin and the anterior vitreous face.

Discussion

The incidence of spontaneous rupture in the anterior vitreous face in aphakics varies in different series between 13·6 and 38% (Harrington, 1952; Kirsh and Steinman, 1954; Jaffe, 1969). There is a definite relationship between these ruptures in the anterior hyaloid and such postoperative complications as secondary glaucoma, vitreous opacification, pupillary changes, corneal damage, and macular oedema. Yet the mechanism of this important phenomenon has remained obscure. Vannas (1932) speculated that the rupture occurred mainly in eyes in which there was previous vitreous pathology and that the region of the pupillary margin was most frequently affected because of mechanical trauma to this area. Reese (1949) stated that the anterior hyaloid membrane may be torn at the time of the surgical intervention without loss of vitreous. Yet this appeared to be infrequent to Kirsh and Steinman (1954), who examined their cases early after surgery for this purpose, and also to us.

The complication appears to occur mainly within 4 weeks after surgery, although it may happen several months after normal healing (Irvine, 1953). The condition may appear in very sedentary patients

Fig. 1 *Passage of dye along the pupillary margin of an aphakic eye with peripheral iridectomy*

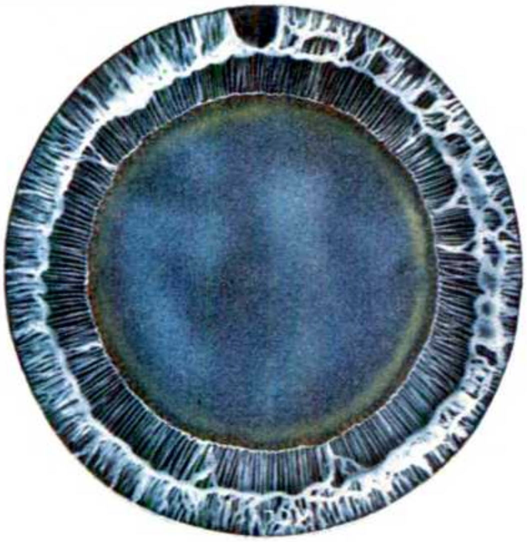
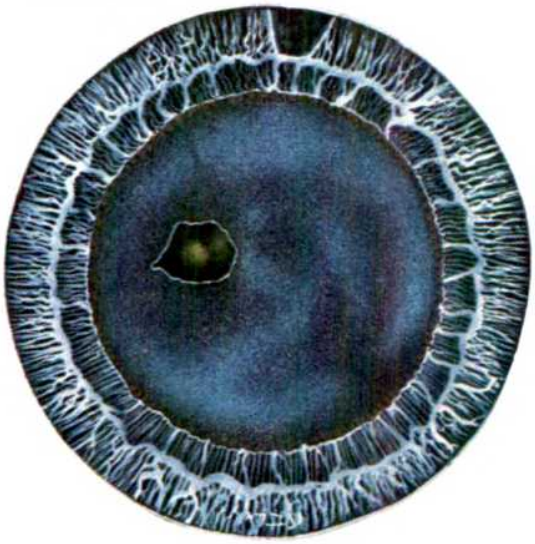


Fig. 2 *Passage of dye through an opening in the vitreous face*



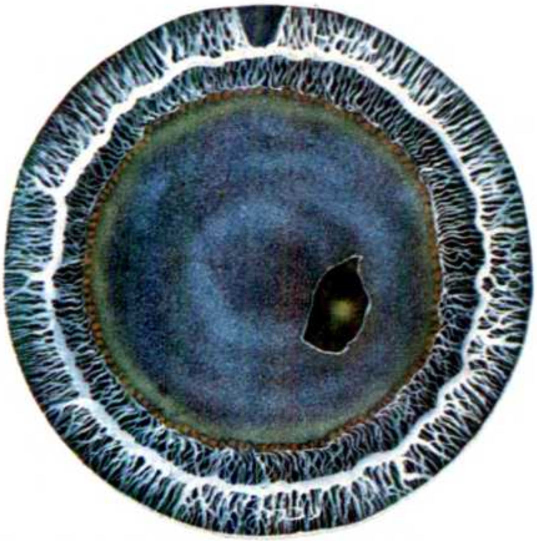


Fig. 3 *Passage of dye along the pupillary margin but not through the vitreous face opening*

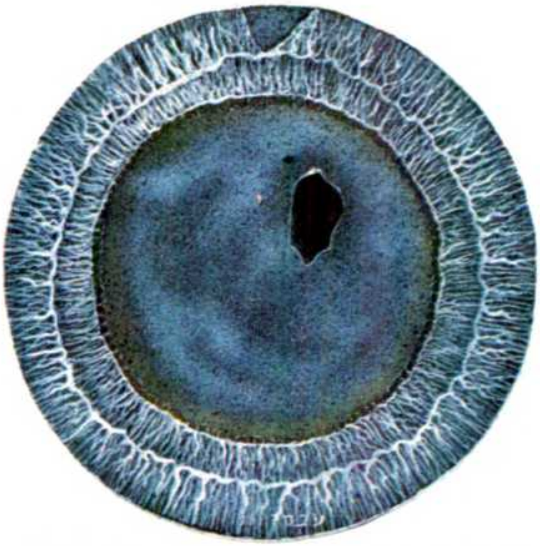


Fig. 4 *Dye percolating through both the pupillary margin and the anterior vitreous face*

and therefore cannot be linked to vigorous activity. Wound leakage has also been considered as a possible factor (Kirsh and Steinman, 1954).

Our study shows aspects that could be of importance in the understanding of the pathogenesis of spontaneous anterior vitreous rupture after cataract extraction. One is the fact that, in a high proportion of aphakic patients with rents in the anterior hyaloid, fluorescein passage to the anterior chamber occurs only through the rent in the vitreous face, while no dye is seen percolating through the pupillary margin, the peripheral iridectomy, or sector iridectomy. This phenomenon indicates a block of the pupil iridectomy by the viscoelastic vitreous. The spontaneous ruptures in the anterior vitreous face could then be interpreted as a compensatory mechanism against pupillary block. Since in the majority of cases the break in the anterior vitreous face occurs in the early postoperative period, it would be reasonable to assume a flow of events in which a small leak in the wound would lead to forward displacement of the vitreous face and a blockage of the pupil and iridectomy. The break in the vitreous face would then be produced by fluid pressure from behind. This way a clinically detectable pupillary block is prevented.

Indirect evidence for this possible mechanism is the observation by Jaffe (1969) in an aphakic patient in which aqueous was shown to penetrate the retrovitreal space through the vitreous substance and not through gaps in the attachment of the vitreous base. Chandler (1951) recognised the importance of inducing surgically an opening in the vitreous face to allow for fluid passage into the anterior chamber in cases of pupillary block leading to malignant glaucoma with an intact vitreous face.

The phenomenon of pupillary and iridectomy block in aphakics could be far commoner than is appreciated, and spontaneous breaks in the anterior hyaloid could represent the tail track of a spontaneous cure. Another aspect of interest in studying the dynamics of fluorescein passage to the anterior chamber is that in eyes with intact vitreous face fluid percolates through the pupil and not through the single peripheral iridectomy.

We are now very particular in sealing the operative wound tightly, and performing 3 peripheral iridectomies. This technique has significantly reduced the incidence of spontaneous breaks in the vitreous face.

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The asymmetrical visual evoked potential to pattern reversal in one half field and its significance for the analysis of visual field defects

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SUMMARY The consistency of the major positive component ($\overline{\text{P100}}$) of the full-field pattern-reversal response provides a clinically valuable and objective means of detecting visual field defects. Its normally symmetrical distribution about the midline of the occipital scalp results from the summation of two highly asymmetric half-field responses, each of which shows the positive component well lateralised with a widespread distribution on the ipsilateral side. Stimulation of each eye in patients with bitemporal and homonymous hemianopias results in two characteristic patterns of asymmetry, named 'crossed' and 'uncrossed' respectively, in which the major positivity is consistently recorded on the side ipsilateral to the preserved half field. Recordings from a patient after occipital lobectomy confirm the authors' previous suggestion that although the major positive component is recorded from the ipsilateral scalp the typical asymmetric half-field response is generated in the contralateral hemisphere.

The wide variability of the cortical evoked potential to flash stimulation in healthy subjects has led some authors to conclude that recording the visual evoked response has little value in clinical diagnosis (Oosterhuis *et al.*, 1969). The use of unstructured flash stimuli in these early studies made it difficult to define the limits of the normal response. In these circumstances objective evidence of even dense hemianopic field defects was relatively hard to obtain (Vaughan *et al.*, 1963; Kooi *et al.*, 1965; Oosterhuis *et al.*, 1969).

In contrast, the consistency of the early components of the transient cortical response to pattern-reversal stimulation has allowed reliable intersubject comparisons to be made. The most prominent and constant component is the major positive wave ($\overline{\text{P100}}$), which has a narrow latency range in healthy subjects and has thus proved of considerable clinical value in detecting and confirming delayed responses in demyelinating optic neuropathy (Halliday *et al.*, 1972, 1973). A further advantage of a pattern stimulus is that it allows the apparent separation of the hemisphere responses, as demonstrated by Cobb and Morton (1970), but the choice of montage and reference electrode is critical in the interpretation of the topography of the response (Michael and Halliday, 1971; Barrett *et al.*, 1976b).

We have recently described the paradoxical lateralisation of the half-field response to pattern-reversal stimulation (Barrett *et al.*, 1976a). The major positive component ($\overline{\text{P100}}$), which has a latency of about 105 ms, was consistently recorded from the electrodes *ipsilateral* to the half field stimulated, while the activity recorded contralaterally was usually much smaller and distinctly different in character (Blumhardt *et al.*, 1977a). Recordings from patients with hemianopic field defects confirm the findings in healthy subjects. The understanding of this consistently asymmetrical half-field response is essential for the interpretation of pattern-evoked potentials recorded from patients with visual pathway pathology.

Methods

Nine healthy persons were used for the study of the normal half-field response. Chlorided silver cup electrodes 9 mm in diameter were fixed to the scalp with collodion. The montage consisted of a transverse chain of five electrodes placed 5 cm above the inion and 5 cm apart, so that two electrodes were situated 5 and 10 cm to either side of a midline electrode. All electrodes were referred to a common midfrontal

Address for reprints: Dr A. M. Halliday, Medical Research Council, Institute of Neurology, National Hospital, Queen Square, London, WC1 reference placed 12 cm above the nasion in the midline.

The stimulus used was a black-and-white checkerboard pattern made up of 50 minute squares projected on to a circular screen which, for full-field stimulation, subtended a radius of 16 degrees from a central fixation point when viewed from a distance of 1 m. For half-field stimulation the screen was masked to produce a semicircular field subtending 16 degrees from the fixation point, which was then situated at the centre of the vertical margin of the field. The brightness levels were 227 cd/m^2 for the white and 8·2 cd/m^2 for the black squares. Pattern reversal was produced once every 600 ms by a rapid lateral displacement of the pattern through one square width, the transition being completed in approximately 10 ms. The occipital potentials were averaged using a PDP-12 computer which was triggered by the pattern reversal, the average response to 200 reversals being recorded in each run. The technique for recording in patients was unchanged except that eccentric fixation was used in some cases with 'macula-splitting' field defects to avoid the effects of a 'pseudofovea'.

Results

HALF-FIELD STIMULATION IN HEALTHY SUBJECTS

The responses from the nine healthy persons all showed features that were essentially similar to those shown by the group average result (Fig. 1). In all subjects the large amplitude surface positive wave with a mean latency of 105 ms ($\overline{\text{P100}}$) was recorded maximally from the electrodes in the midline and ipsilateral to the half field stimulated, the distribution of this component thus being largely responsible for the consistently asymmetrical half-field response. The ipsilateral waveform was further characterised by two surface negative waves ($\overline{\text{N75}}$, $\overline{\text{N145}}$) which immediately preceded and followed the positive wave, the whole NPN complex being widespread over the ipsilateral scalp. A steep voltage gradient was seen near the midline and the response recorded at the contralateral electrodes varied from small amplitude deflections, which were too near the background noise level to be clearly defined, to a triphasic PNP complex which was often best seen in the most lateral (10-cm) channel. The major components of this complex appeared to be at similar latency but of opposite polarity to the ipsilateral components (Fig. 1). There was a considerable subject-to-subject variation in the presence and relative amplitude of these contralateral waves, the third component ($\overline{\text{P135}}$) in particular tending to dominate the contralateral response in an occasional individual. In such a case it is important not to confuse this contralateral positive component, which has a distinctly different latency and distribution, with the ipsilateral $\overline{\text{P100}}$.

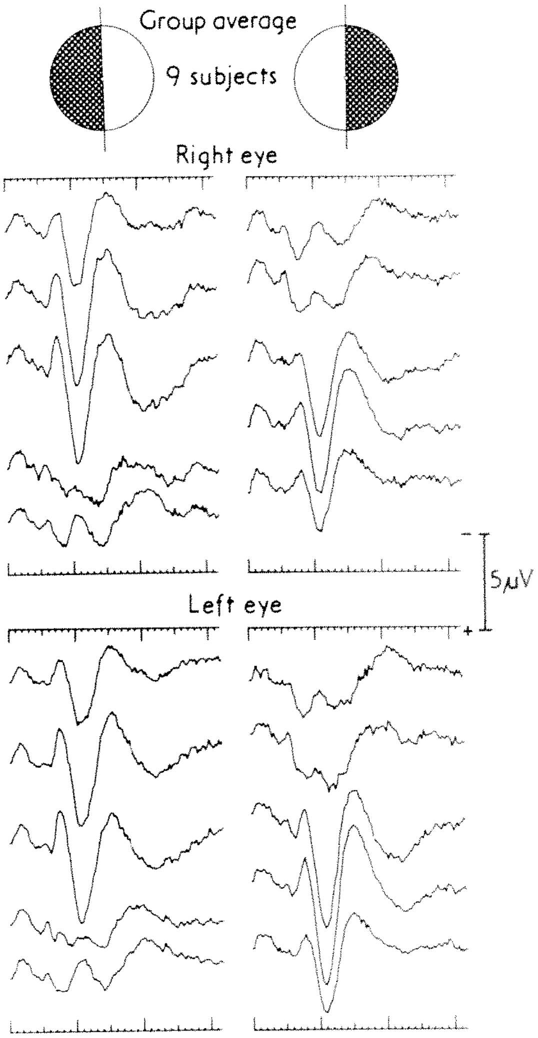

Fig. 1 *Group average of monocular half-field responses of nine healthy subjects. Stimulated half fields shown checkered. Channels from top to bottom represent a transverse chain of five electrodes placed symmetrically at 5-cm intervals from left to right across occipital scalp (see head diagrams Figs. 2–5). Time scale for this and all other figures, 10, 50, 100 ms marks*

The study of the normal half-field response in the nine subjects reported in this paper has been subsequently confirmed in 32 healthy subjects, all of whom show essentially similar features. A more detailed account of the relationships between the ipsilateral and contralateral responses evoked by half-field stimulation is in preparation (Blumhardt *et al.*, 1977b).

FULL-FIELD STIMULATION IN HEALTHY SUBJECTS
When full-field stimulation is performed using the same electrode montage, clearly the recorded responses must be a complex of the responses from both hemispheres. In our healthy subjects there was no consistent lateralisation of the full-field response related to the eye stimulated, the major components usually being fairly symmetrically distributed about the midline. This would be predicted from the usually similar amplitudes of the major components of the left and right half-field responses. Where these amplitudes were dissimilar on the two sides of the scalp minor full-field asymmetries were seen. These asymmetries are the same for stimulation of each eye, indicating that they are most probably due to anatomical differences between hemispheres. A fuller account of these hemisphere differences is in preparation (Barrett *et al.*, 1977).

From Fig. 1 it can be predicted that the addition of corresponding channels from each half-field response will produce a large amplitude response in the midline, since both half-field responses have a large amplitude positive component (P100) in the midline channel. In the lateral channels the addition of components of opposite polarity and usually unequal amplitude will result in the voltage of the summated response falling off to either side of the midline—for example, the addition of the large ipsilateral P100 from the left channels of the left half-field response, with the small negative wave (N105) from the contralateral channels of the right half-field response, produces a resultant positive wave which is reduced in amplitude. When the corresponding components from each half field are of about the same amplitude the full-field response would appear predominantly in the midline channel while the lateral channels will be relatively flat. This theoretical prediction from the algebraic summation of the half-field responses closely approximates the actual responses recorded from full-field stimulation in healthy subjects, an example of which is shown in Fig. 2.

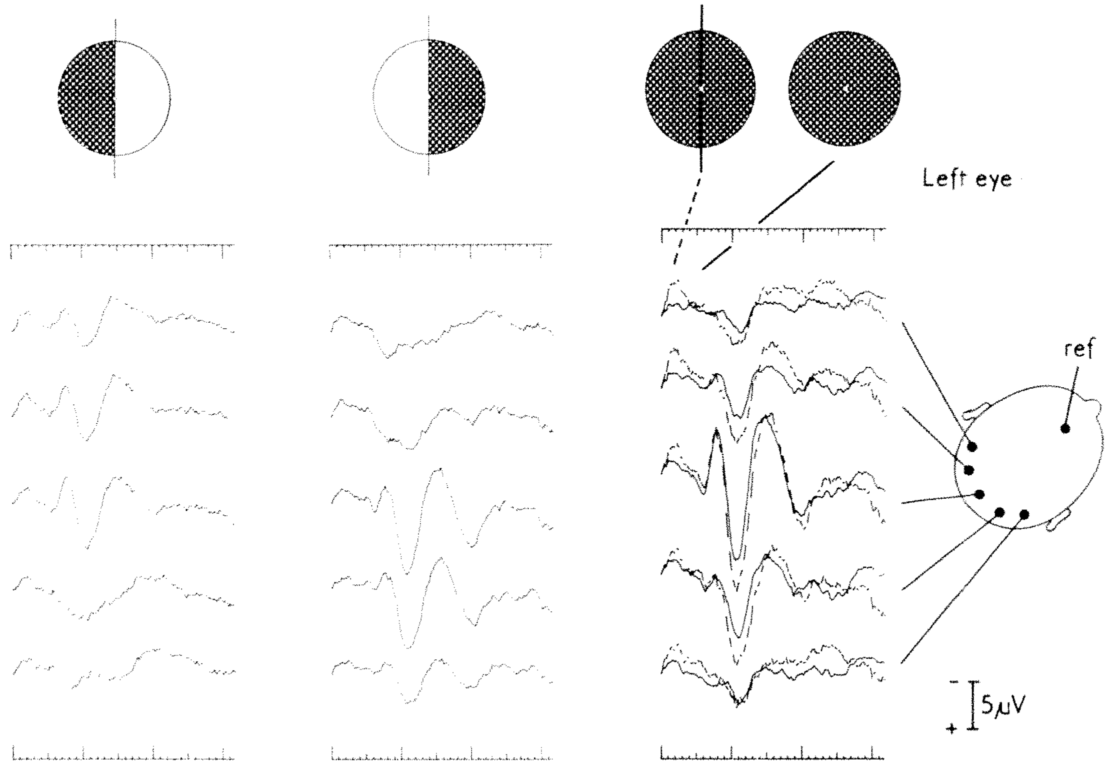

Fig. 2 *Comparison of monocular full-field response with summated half-field responses in one healthy subject. The asymmetric left and right half-field responses are shown on left; the algebraic summation of these two responses is shown on right (dotted line) superimposed on separately recorded full-field response (solid line)*

ASYMMETRIES IN PATIENTS WITH HEMIANOPIC FIELD DEFECTS

Homonymous hemianopia

The results of stimulating a patient with a left homonymous hemianopia are shown in Fig. 3. This case was recorded after surgical removal of an arteriovenous malformation at the right occipital pole. The resulting left half-field defect was a dense homonymous 'macula-splitting' scotoma which extended out from the fixation point to about 25 degrees. Our 0 to 16 degree checkerboard stimulus was thus well within the scotoma to the left of the midline. Full-field stimulation out to 16 degrees could therefore produce a response only from the preserved right half-field. Monocular full-field stimulation resulted in an asymmetric response which is the same for each eye. The typical ipsilateral complex (NPN) of the normal right half-field response is clearly seen in the midline and right-sided channels, while contralaterally the channel 5 cm from the midline shows only a small positive deflection and the most lateral channel is flat. Half-field stimulation, in this case using 2 degree eccentric fixation to allow for a pseudofovea, confirms the defect in two ways—firstly, by demonstrating that there is no response from the affected half-field and, secondly, by the similarity between the full-field and intact half-field responses (Fig. 4). The reduced size of the response from the right half-field, as compared with that in the full-field response, is no doubt a consequence of the reduction of the stimulus area adjoining the vertical meridian associated with the eccentric fixation. This type of asymmetry, which is the same for stimulation of each eye, we have called an 'uncrossed' asymmetry (Barrett *et al.*, 1976a; Halliday *et al.*, 1976).

Bitemporal hemianopia

In patients with bitemporal field defects the asymmetry of the full-field response is reversed for each eye, as shown by the records in Fig. 5. In the response from the left eye the major positive component

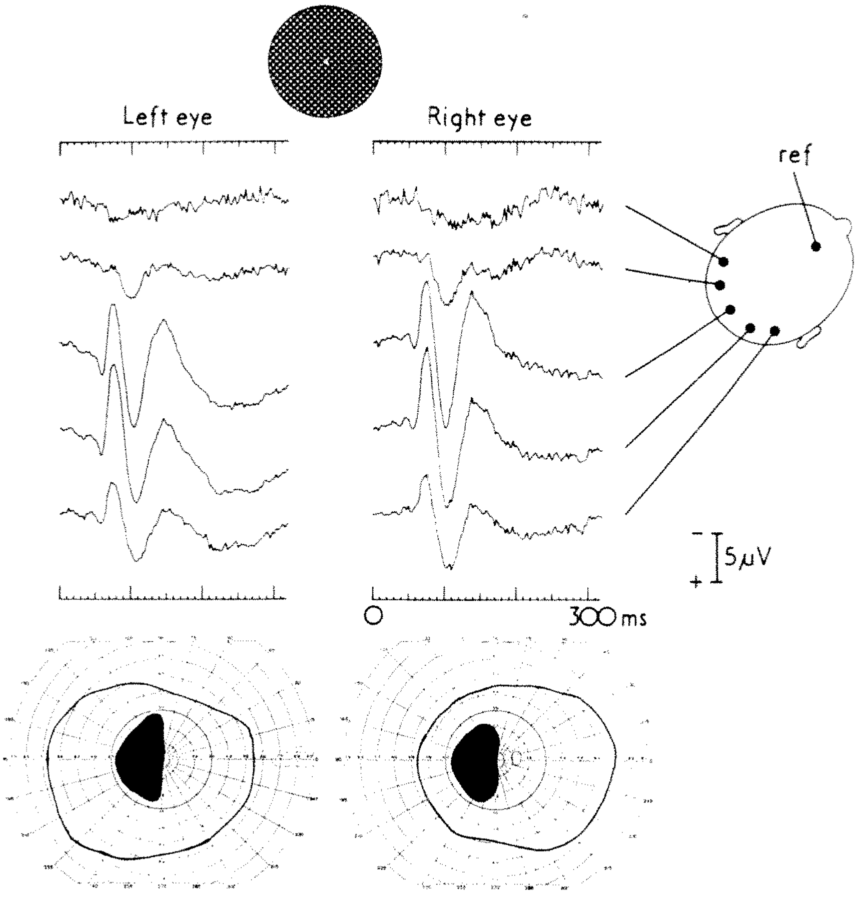

Fig. 3 *Monocular full-field stimulation of patient after subtotal right occipital lobectomy. Goldmann visual fields show total homonymous 'macula-splitting' scotoma extending to about 25 degrees radius. Note that the asymmetry of the response is the same on stimulation of each eye—that is, it is 'uncrossed'*

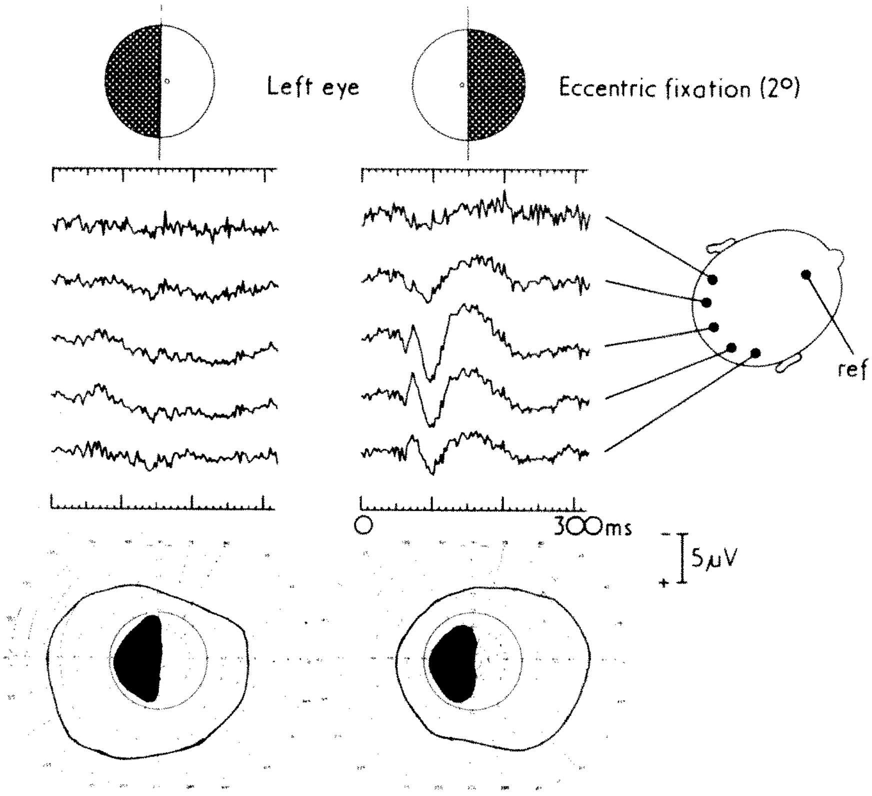

Fig. 4. *Half-field stimulation using two degree eccentric fixation in patient whose full-field responses are shown in Fig. 3. Pattern-reversal within the scotomatous field defect produces no response detectable above the background noise (left hand record). Pattern-reversal within the preserved right half field produces a typical 'ipsilateral complex' (NPN) from the scalp overlying the hemisphere with the surgical defect. Channels over intact left hemisphere are relatively flat. The smaller amplitude response when compared with that from full-field stimulation is due to eccentric fixation*

($\overline{\mathrm{P100}}$) is clearly seen in the right-sided and midline channels—that is, from the scalp ipsilateral to the intact visual half field—while in the left-sided channels the $\overline{\mathrm{P100}}$ has been replaced by a complex of opposite polarity with, in this case, a particularly prominent second positive wave. The absence of an ipsilateral response, particularly the $\overline{\mathrm{P100}}$ from the left-sided channels, indicates that the left visual half field is defective. For the right eye the distribution of these components is reversed with the ipsilateral $\overline{\mathrm{P100}}$ being seen over the left side of the scalp accompanied by a PNP complex contralaterally. This type of asymmetry, which reverses on full-field stimulation of each eye, we have called a 'crossed' asymmetry (Barrett *et al.*, 1976a; Halliday *et al.*, 1976).

Discussion

A feature of many previous studies of patients with hemianopic field defects, including recent reports of the use of pattern stimuli by Wildberger *et al.* (1976), and Celesia and Daly (1976), has been the assumption that the decreased response should be recorded from the scalp electrodes situated contralateral to the visual field defect. This implies that the maximal, or at least optimal, response to stimulation of a normal half field will also be recorded from the contralateral electrodes, but no detailed description of the transverse distribution of full- or half-field responses in normal subjects had been reported in these papers. Our own studies show that this implication is not confirmed by the experimental findings, the major positivity being recorded ipsilaterally (Barrett *et al.*, 1976a). These conclusions are confirmed by an examination of the records in the recently published report by Shagass *et al.* (1976), although owing to the much lower intensity of their pattern stimulus the $\overline{\mathrm{P100}}$ component there appears as a $\overline{\mathrm{P125}}$ wave.

With the use of a distant midline reference and 'monopolar' recording we have found that all normal half fields tested to date produce a clear positive wave at about 100 ms which is transversely distributed over at least 10 cm of the ipsilateral scalp (Barrett *et al.*, 1976a). In a few individuals the $\overline{\mathrm{P100}}$ of the half-field response may spread slightly across the midline, but it invariably attains its maximum amplitude in the midline or ipsilateral channels. Together with the two surface negative waves

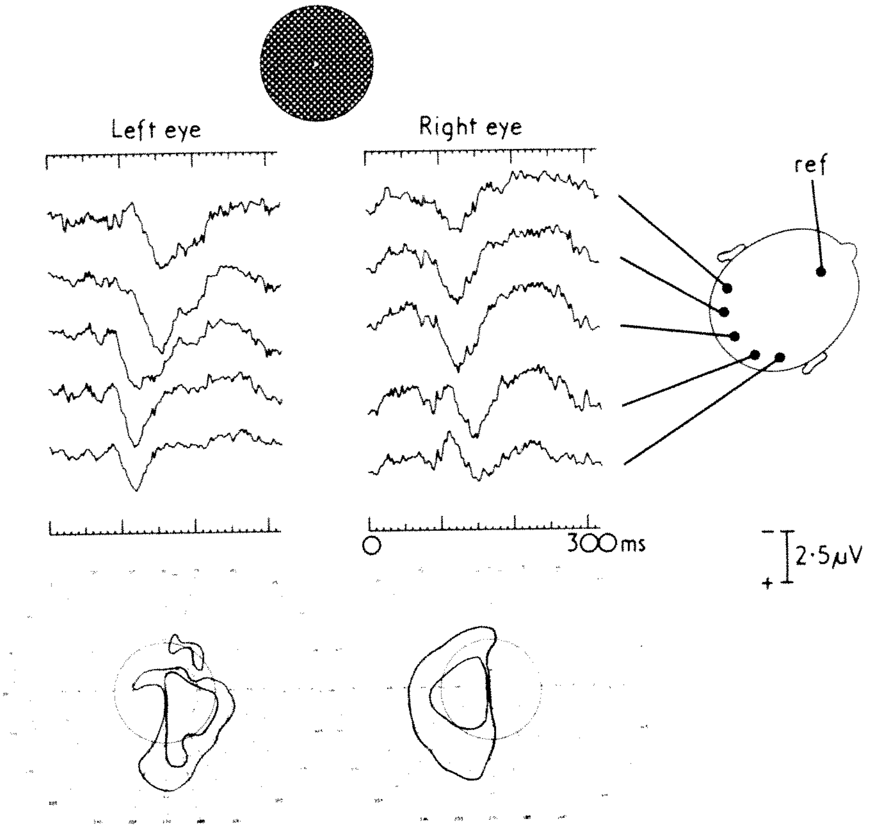

Fig. 5 *Example of a 'crossed' asymmetry recorded from patient with chiasmal compression due to pituitary adenoma. Goldmann perimetry showed irregular bitemporal hemianopia. Note that the positive wave in the contralateral channels, which is particularly prominent in the response from the left eye, is the contralateral component ($\overline{\mathrm{P135}}$) seen in the half-field responses of normal subjects. This wave should not be confused with the ipsilateral positivity ($\overline{\mathrm{P100}}$)*

immediately preceding and following the positivity, which are slightly less consistent, this positive wave makes up an ipsilateral triphasic complex which provides a useful indicator of the integrity of the visual half field. By contrast, the activity recorded from the scalp contralateral to the half field stimulated appears more variable, with components which are often small and sometimes absent or hidden, and of opposite polarity to the corresponding ipsilateral waves at similar latency.

We have proposed that the unexpected lateralisation of the major positive component ($\overline{\mathrm{P100}}$) is related to the mesial location of the response generators on the hemisphere contralateral to the field stimulated, the ipsilateral electrodes being optimally placed to record a response from the posteromedial aspect of the contralateral hemisphere (Barrett *et al.*, 1976a). The possiblity remained, however, that part of the response could be generated in the ipsilateral hemisphere, perhaps through the operation of the transcallosal connections (Beauchamp *et al.*, 1976). This idea is not supported by the case demonstrated in Fig. 3. The normal amplitude $\overline{\mathrm{P100}}$ which forms part of a typical 'ipsilateral complex' (NPN) is recorded from the channels directly over the hemisphere from which the tip of the occipital lobe has been excised. Hence it is unlikely to be generated on this side. Stimulation of the intact hemisphere, using 2 degree eccentric fixation to avoid stimulating the area of the field which may be expected to have transcallosal connections, clearly shows that the characteristic NPN complex is still recorded from the scalp ipsilateral to the half field stimulated (Fig. 4). These results indicate that although the $\overline{\mathrm{P100}}$ is recorded in the midline and ipsilateral channels it is generated in the hemisphere contralateral to the half field stimulated, in agreement with our previous suggestion (Barrett *et al.*, 1976a). Thus we have no evidence to support the proposal of Wildberger *et al.* (1976), who recorded a small ipsilateral steady-state response to an 8-Hz pattern-reversal stimulus in one half field and attributed it to transmission by intercallosal connections. Further, from recordings made on patients with more extensive occipital lobectomies (Blumhardt *et al.*, unpublished) it is clear that both the ipsilateral complex (NPN) and contralateral activity (PNP), while being recorded from opposite sides of the scalp, are generated in the hemisphere contralateral to the half field stimulated.

We have previously emphasised the critical importance of the montage and choice of reference electrode in this type of topographic study (Michael and Halliday, 1971; Barrett *et al.*, 1976b). For example, the use of a transverse chain with bipolar linkages not only results in a loss of information when component amplitudes are similar at each electrode in the chain but, more seriously, can cause erroneous localisation of the maximal response (Barrett *et al.*, 1976a; Shagass *et al.*, 1976). The use of a reference placed to one side of the midline, as adopted by some workers in this field (Jeffreys and Axford, 1972a; 1972b; Wildberger *et al.*, 1976) is inappropriate for the study of the transverse distribution of the asymmetric half-field responses. Since the ipsilateral response is widespread over the scalp to one side of the midline the ear reference is far from indifferent and will tend to exaggerate or reduce asymmetries on opposite sides depending on which hemisphere is stimulated. For this reason an ear reference is an unwise choice for the detection of field defects.

The placement of the occipital recording electrodes is also critical. The midline of the occipital scalp is an area of rapid voltage change. Recordings made from electrodes in or near the midline will therefore exhibit large differences in waveform with small changes in location on the scalp, and are thus unlikely to provide accurate information about hemianopic field defects unless augmented by information from more laterally placed electrodes. Asselman *et al.* (1975) found normal latency pattern evoked responses in three cases with hemianopia due to optic radiation lesions. Their conclusion that a macula-splitting hemianopia will not affect the latency recorded at a midline electrode is based on insufficient information, as the midline channel may be distorted in hemianopia or in the half-field response in normal subjects (Blumhardt *et al.*, 1977b). Celesia and Daly (1976), using a combined technique of both flash and pattern-reversal with the 10–20 system of electrode placement, also found normal visual evoked responses in five patients with hemianopia. We do not consider that the commonly used 0_1 and 0_2 electrodes of the 10–20 system are suitable for the study of visual field defects, because they are situated too close to the midline. These studies emphasise that a multichannel recording of the distribution and waveform of the response over the lateral scalp rather than isolated amplitude and latency measurements is essential for accurate confirmation of pathological field defects.

The use of a circular stimulating field with central fixation necessarily produces a response which is a summation of the complexes produced by the two hemispheres. The two highly asymmetric half-field responses, when they are recorded separately and algebraically summated, closely approximate the response to full-field stimulation (Fig. 2). Thus a defect of one half field should 'unmask' the asymmetry of the other intact half-field response (NPN) which will then dominate the record, either flat channels or the triphasic complex of opposite polarity (PNP) indicating the side of the defective field. Two major types of asymmetry have emerged—namely, 'uncrossed' and 'crossed'—indicating homonymous and heteronymous hemianopias respectively. In dealing with homonymous hemianopias it is important to recognise the anatomical asymmetries that may occur in a proportion of healthy individuals. If full-field stimulation is used as a screening test these minor asymmetries can then be further tested with half-field stimulation. With this technique we have not encountered any difficulty in separating dense hemianopics from normals. In this respect the pattern stimulus marks a major advance on flash stimulation. With a 'crossed' asymmetry, which does not occur in normal individuals, one does not have to contend with the hemisphere differences and any record showing these features is strongly suggestive of a chiasmal lesion. On at least two occasions we have been able to indicate chiasmal compression in patients with gross reduction of visual acuity, ambiguous perimetry, and negative EMI scans in whom subsequent contrast studies have shown compressive space-occupying lesions. While this technique is accurate in recognising dense hemianopic visual field defects there is also some evidence from our recordings on patients to suggest that the method may be more sensitive than routine perimetry in detecting more subtle lesions of the visual pathways. In the published study of compressive lesions of the anterior visual pathways, for instance, two patients showed asymmetric responses without any associated field defect being demonstrable (Halliday *et al.*, 1976).

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Pseudoexfoliative disease of the lens: a study in electron microscopy and histochemistry

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SUMMARY The anterior lens capsule in pseudoexfoliative (PE) disease has been investigated with scanning electron microscopy and transmission electron microscopy. It shows several distinct zones which correlate with those seen clinically. True exfoliation of the anterior lens capsule is shown as an integral pathologic feature of PE disease.

PE fibrils are mixed with various degraded cell products, including organelles, of which uveal pigment granules are the most frequent. Sheets of degenerating iris pigment epithelium as well as individual cells are often firmly adherent to the pre-equatorial lens capsule and zonules.

PE fibrils on the capsule are 35 to 40 nm in width, often showing several subunit filaments about 10 nm wide. PE filaments forming vertical bundles in the pre-equatorial capsule are 10 nm wide, but show little tendency to aggregate laterally. Histochemical and ultrastructural properties of both types of PE fibril and those of the capsular inclusions suggest that they are closely related fibrillar proteins. PE fibrils share some of the characteristics of amyloid but are not identical substances. Nevertheless, a similar mechanism of synthesis is suggested. The participation of non-lenticular sites in the formation of PE fibrils is not precluded by this hypothesis.

Pseudoexfoliative (PE) disease of the lens, a disorder of widespread geographic and racial distribution, is of unknown aetiology. It has been demonstrated in the Bantu tribe in South Africa that a subtle radial striation of the anterior lens capsule, occurring in early or middle adult life, represents an early slit-lamp sign of this disease (Bartholomew, 1971), but the classical manifestations are almost exclusively geriatric. Vogt (1925) believed that the greyish frosting material lying on the anterior lens surface and on other structures bathed in aqueous was produced by vacuolation and exfoliation of the superficial capsule. A similar mechanism involving the zonular lamella has been proposed by Gifford (1957) and more recently by Sugar (1976). Ashton *et al.* (1975), however, have noted that there is no transmission electron micrographic (TEM) evidence for the existence of a zonular lamella except in the peripheral region of the lens, where the zonules insert. The concept of an exfoliative process is nevertheless strongly supported by slit-lamp microscopy, which often shows the PE material to be flaking or rolling up as a layer central to the zonular insertion. In contrast, PE material in sections stained in haematoxylin and eosin is seen usually as discrete, pink bush-like masses attached in either a sessile or pedunculated manner to the anterior lens surface but often without evidence of capsular dehiscence. This appearance led Busacca (1928) to interpret them as *deposits* of an unidentified material of unknown origin. An attempt to synthesise these somewhat divergent observations and to distinguish the disorder from true (thermal) exfoliation of the lens capsule resulted in the introduction by Dvorak-Theobold (1954) of the semantically confusing name 'pseudoexfoliation', which is in general use.

The recent (TEM) studies of Ghosh and Speakman (1972) have indicated that a true shedding of the superficial capsule may indeed occur. Davanger and Pederson (1975) and Davanger (1975) using TEM and scanning electron microscopy (SEM) have likewise shown that the PE excrescences rest on a 'basal lamina', which has a marked tendency to curl up.

The cells which synthesise PE material have not yet been identified in spite of several transmission electron microscopy studies involving the anterior segment of the eye. Thus, Ashton *et al.* (1965), who

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examined lens, iris, and ciliary body in PE disease, were unable to determine a site of origin. They did note, however, a pathognomonic feature of this disorder, namely, the presence of PE-like material in the deep layer of the lens capsule immediately anterior to the equator. This deep layer was detected independently by Bertelsen *et al.* (1964), who also observed that it was often vertically striated under the light microscope. TEM showed that the striations correspond with bundles of fibrillar material located in deep pits of the adjacent anterior lens epithelium. This latter appearance persuaded these authors that the pre-equatorial zone of the anterior lens epithelium is a primary site for the production of PE material.

The pre-equatorial zone of the normal lens capsule contains numerous inclusions which have been shown by Bertelsen and Ehlers (1969) and Dark *et al.* (1969) to have TEM and histochemical properties similar to PE fibrils. Capsular inclusions are unduly elongated and present in profusion in PE disease. These and other observations led Dark *et al.* (1969) to postulate that the lens production of capsular inclusions is accelerated in some way in PE disease, and that a similar process leads to synthesis of PE fibrils both within and outside the lens capsule. Ghosh and Speakman (1973, 1974) in TEM studies noted distinctive changes in the epithelia of the iris and ciliary body which led them to propose these as additional primary sites of PE fibril manufacture.

Ringvold (1973a) observed that PE material was also deposited in the walls of conjunctival capillaries, a finding confirmed and extended by Ghosh and Speakman (1976). Using iris fluorescence angiography, Vannas (1969) demonstrated abnormal vessels leaking fluorescein. Hence it was suggested that PE material is blood-borne, diffusing into the anterior chamber through walls of diseased vessels of the iris.

The present study is an attempt to clarify the SEM and TEM correlates of well-known clinical observations. At the same time the alleged role of the pre-equatorial lens epithelial cells in the pathogenesis of PE disease is evaluated further.

Methods and materials

SCANNING ELECTRON MICROSCOPY

Six cataractous lenses were obtained from 5 septuagenarian patients who had normal ocular tensions. All were studied by slit-lamp microscopy after mydriasis. Patient 1 had unilateral PE disease. Both lenses were obtained, the apparently unaffected lens to act as control. Patients 2, 3, and 4, who had bilateral PE disease, provided another 3 lenses. The sixth lens, from Patient 5, clinically unaffected with PE disease, provided a further control.

Lenses were extracted with a cryoprobe without using alpha-chymotrypsin. They were fixed in cold, phosphate-buffered 2·5% glutaraldehyde for 1 hour, then osmified before dehydrating in graduated acetones. Finally, absolute acetone was removed by critical point drying with liquid carbon dioxide. The desiccated lenses were then vacuum-coated with carbon followed by gold-palladium before examination in an ETEC Autoscan scanning electron microscope which had been previously calibrated.

TRANSMISSION ELECTRON MICROSCOPY

Eight cataractous lenses from patients afflicted with PE disease were obtained at operation. Three lenses were immediately fixed in phosphate-buffered 2·5% glutaraldehyde for 2 hours. Osmification followed, and then small pieces of anterior lens capsule were excised from the various zones before embedding in epoxy resin. These sections were stained with uranyl acetate and lead citrate before examination under an RCA transmission electron microscope.

HISTOCHEMISTRY

Three cataractous lenses affected with PE disease were fixed in formalin and then embedded in paraffin. Sections from these lenses were stained with haematoxylin and eosin and a number of special stains to be mentioned alongside the results. Two unfixed cataractous lenses showing typical clinical features of PE disease were cut frozen, and the sections were stained with fluorescein antibody conjugates for lambda and kappa immunoglobulin light chains.

Observations

SCANNING ELECTRON MICROSCOPY

Apart from zonular remnants the anterior surfaces of the 2 clinically normal lenses have a faint granular texture at high magnification.

The 4 lenses clinically affected with PE disease were similar in general appearance and are described together. The general topography of the anterior lens surface in PE disease can be best seen at low magnification (Fig. 1). The various zones correlate well with the appearances of slit-lamp microscopy, showing a greyish central zone separated by a featureless intermediate annulus from the region of granular deposits, then a peripheral zone, and finally a pre-equatorial zone. The central zone comprises a layer of fibrils (40 to 60 nm in diameter) in which are embedded numerous smooth-surfaced ovoid bodies. The ovoid bodies are orientated vertically and vary in height from 0·5 to 1·0 μm and

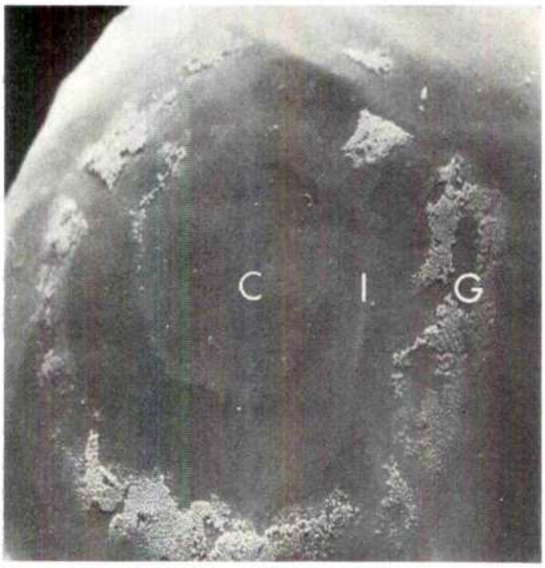

Fig. 1 *Anterior surface of the lens in PE disease, illustrating central zone* (C), *intermediate zone* (I) *and the granular zone* (G). *SEM* ×7

are 0·25 to 0·50 μm wide (Fig. 2). At the periphery of the central zone are variable heaped-up aggregates of fibrillar material. Similar but sparser elements are found in the intermediate zone. The granular zone, at low magnification, is seen as a grove of vegetations (Fig. 3 inset) closely grouped together. The largest vegetations (15×15 μm) are found in the middle of this zone with a gradual decrease in size towards the edges, where the smallest (5×3 μm) are found. The vegetations, which are occasionally joined together by a few fibrils 40 to 60 nm wide (Fig. 3), are for the most part discrete. Each comprises a skein of closely-knit fibrils interspersed with numerous ovoid bodies; these components have similar dimensions to those in the intermediate and central zones. The lens surface in this zone, where it can be viewed, is overlaid with occasional fibrils on which ovoid bodies can be seen usually singly but sometimes grouped. The rolled appearance of the inner edge of this zone is produced by a peeling and curling up of the surface layer, to which the vegetations are attached (Fig. 4)

Here and there vegetations similar to those seen in the granular zone encrust occasional zonular remnants.

TRANSMISSION ELECTRON MICROSCOPY

Central Zone.—Sections from the central zone show that the superficial layer of the capsule has a somewhat denser structure than the main part. This surface zone is often separated by a rarefied seam from the main bulk of the underlying capsule. Its attachment is evidently tenuous, so that in places it is dehiscent and rolled up. Embedded in this surface layer are a few membrane-clad organelles, most of which are clearly identifiable as pigment granules. Occasional mounds of unidentified amorphous

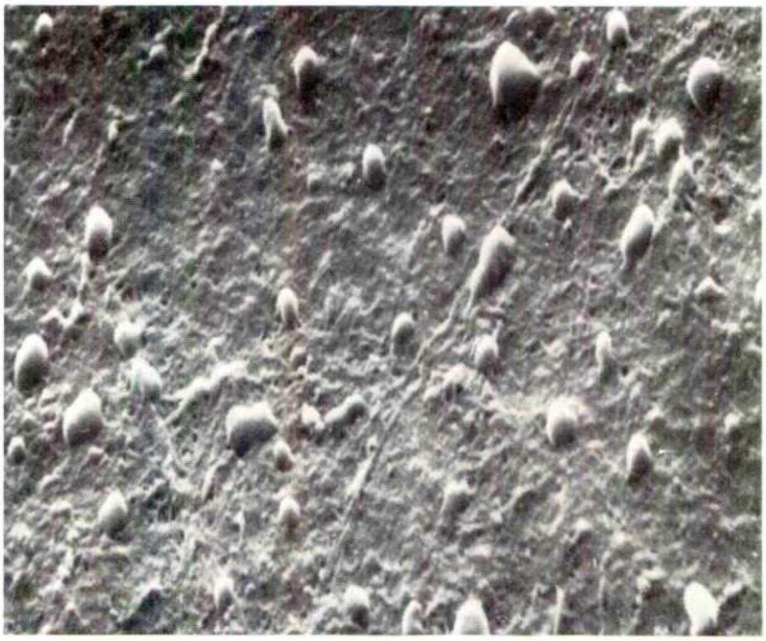

Fig. 2 *Anterior surface of the lens in PE disease. Central zone depicting meshwork of fibrils with embedded ovoid bodies. SEM* ×3550

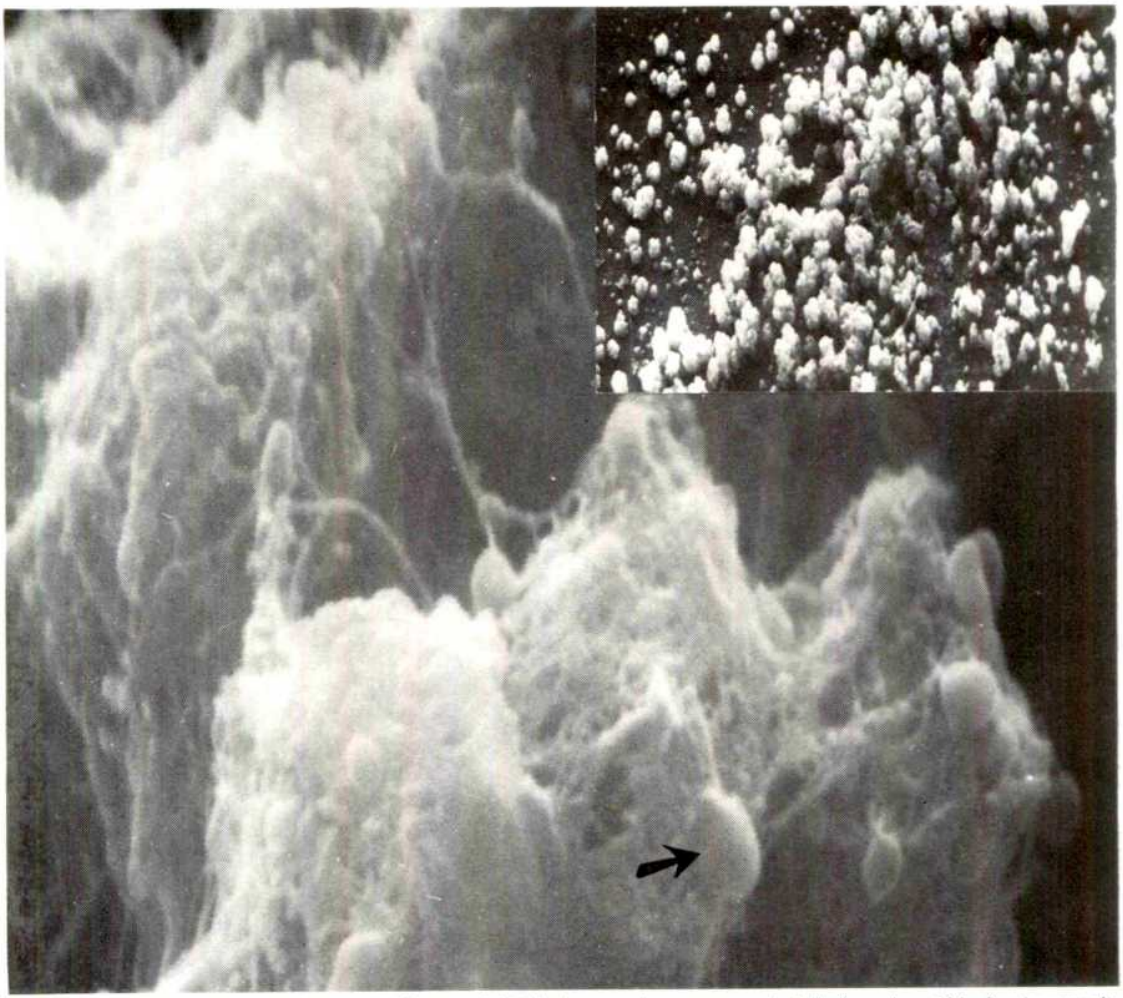

Fig. 3 *Anterior surface of the lens in PE disease. Individual vegetations composed of fibrils and ovoid bodies* (arrowed). *SEM* ×6100 *from the granular zone* (inset). *SEM* ×275

electron-lucent material are also present. These structures embedded in the surface correspond both in dimensions and in frequency of distribution with the ovoid bodies seen in SEM. A thin layer of PE fibrils lies flat on the surface. They are rarely aggregated in a bush-like arrangement.

Granular Zone.—As in the central zone a thin layer of PE fibrils lies on the superficial capsular lamellae, which are somewhat more compact than the rest of the capsule. This tendency for this surface layer to split away from the rest of the capsule and in some instances to roll up like a scroll is marked (Figs. 5 and 6). Resting on the superficial capsular layer are the vegetations (Fig. 7*a*). They are composed of intertwined PE fibrils, among which are regularly found a variety of organelles, including pigment granules, mitochondrial elements, and fragments of cytoplasm (Fig. 7*b*). PE fibrils, which are best studied in the vegetations of the granular and pre-equatorial zones, vary in width from 10 to 40 nm (the latter being much more frequent), while cross-striations occur at 20 nm and appear to extend somewhat behind the main body of the fibril, giving it a characteristic smudgy outline. At high magnification it is sometimes possible to determine that the larger PE fibrils are composite, consisting of several subunits which are about 10 nm wide (Fig. 8).

Pre-equatorial Zone.—Zonular fibres when present in this region are encrusted with accumulations of PE fibrils, especially on their lateral aspects. The

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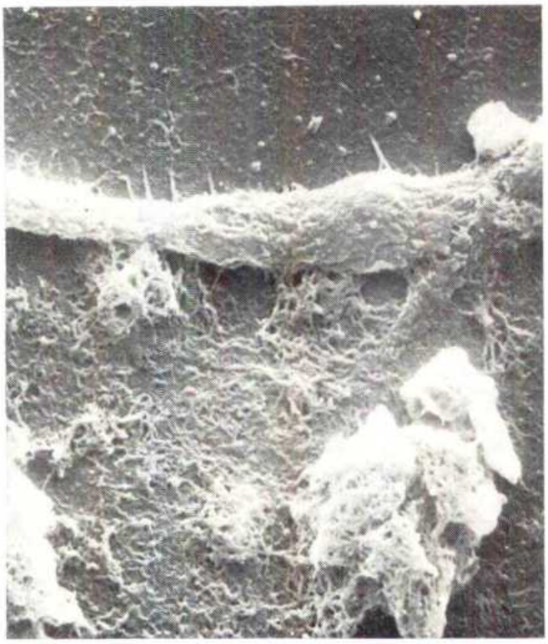

Fig. 4 *Anterior surface of the lens in PE disease. Granular zone with vegetations lying on layer of fibrils which has rolled edge.* *SEM* × 4010

zonular fibrils exhibit no intrinsic abnormalities even under high magnification. For the most part PE and zonular fibrils are not intermingled but there are occasional foci in which a degree of admixture occurs. PE fibrils lie on the capsule sometimes as a layer and at other times as vegetations. As in the other zones, numerous organelles are mixed in with PE fibrils. In 3 lenses the presence of sheets of iris pigment epithelial cells adherent to the PE material covering the zonules was noted.

The capsule itself contains numerous large granular inclusions. The characteristic deep, striated or amorphous layer lying next to the epithelium is seen in many sections from this region (Fig. 9). This layer consists of rarefied capsular material, traversed by compact bundles of fibrils which splay out vertically from pits in the underlying epithelium. These vertical fibrils are about 10 nm wide. Finger-like cytoplasmic processes extend from the epithelial cells into the striated band. It is not possible to determine whether certain organelle-like elements in this layer lie free or are produced by cutting these processes obliquely. The underlying epithelium shows variable vacuolation but no evidence of increase in organelles. Multilaminar basement membrane production is evident in some parts of the amorphous layer, but this is not a regular feature.

HISTOCHEMISTRY

In haematoxylin and eosin preparations PE material and the capsule proper are stained pink while the striated band has a bluish tinge. Gomori's chrome haematoxylin colours the PE material on the lens surface and the capsular inclusion (Fig. 10) and the striated band a variable dark blue (Fig. 11*a*). The striations are intensely stained as black lines in vertical sections but as black dots in tangential cuts. The zonular fibres are also blackened by this method.

Congo red dichroism is not present in any of the sections examined. Sections stained with thioflavins T and S were examined by ultraviolet light. Green fluorescence is observed in PE material on the anterior surface of the capsule and capsular inclusions (Fig. 10 inset) and in the striated band (Fig. 11*b*). The striations but not the intervening capsular material are stained, appearing as bright vertical lines or dots, the appearance depending on whether perpendicular or tangential sections are studied. Zonular fibres are unstained. No fluorescence of the capsular PE materials or inclusions is noted after treating unfixed frozen sections with fluorescein antibody conjugates which had been raised to lambda and kappa immunoglobulin chains. These con-

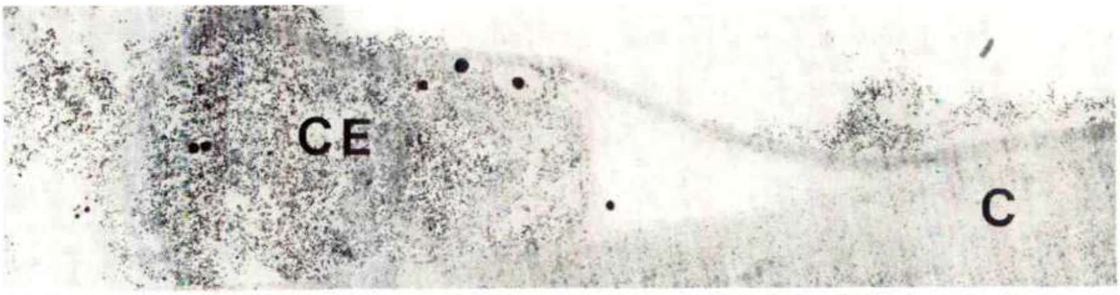

Fig. 5 *Granular zone in PE disease. Dehiscence of the capsule* (C) *has resulted in a scroll-like composite of superficial capsule, PE fibrils and various organelles. Exfoliated capsule* (CE). *TEM* × 11 600

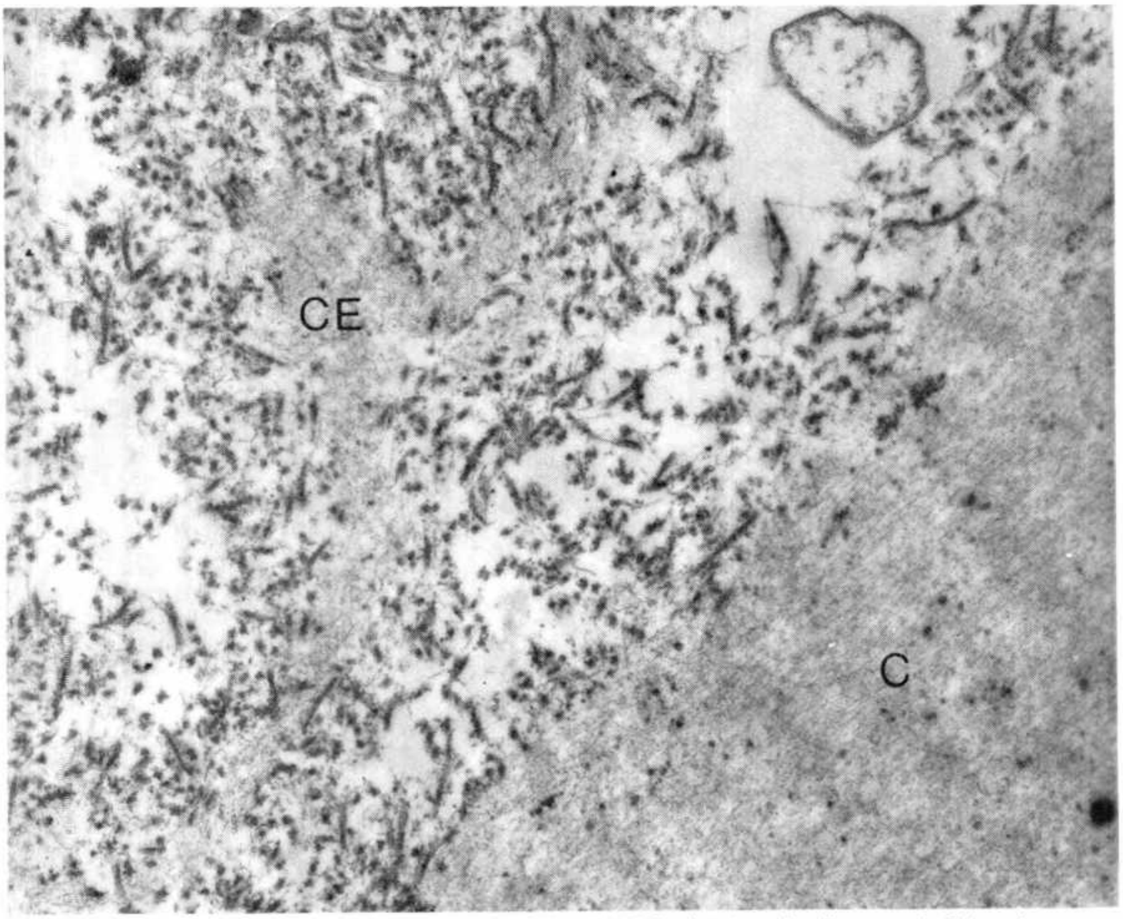

Fig. 6 *Detail from Fig. 5 showing exfoliated capsule* (CE) *with PE fibrils intimately adherent to it.* C *is main capsule. TEM* × 26 780

jugates produced intense cytoplasmic fluorescence in plasma cells which were present in bone marrow sections used as controls.

Comments

The several zones of the anterior lens capsule in PE disease are readily discernible by slit-lamp microscopy. At high magnification the granular zone is seen as fine white dots (the vegetations) on a greyish translucent background layer. The central edge of this layer is often rolled up in a scroll-like fashion. A similar separation of the edges of the central zone is sometimes seen. Indeed, we have personally observed exfoliation along with faint radial striae as one of the earliest biomicroscopic features of this disease. The present TEM and SEM studies indicate that this tendency of the granular and central zones to desquamate is a true dehiscence of the superficial capsule for which the term 'pseudoexfoliation' is clearly inappropriate. Exfoliation of the superficial lens capsule was also noted in the recent TEM studies of Ghosh and Speakman (1972) and of Sugar (1976).

The central zone in PE disease, present in about 90% of patients with this disorder, was examined with SEM by Benedikt *et al.* (1973), who found a verrucose surface texture and noted a tendency for the disc edges to curl up. TEM observations by the same authors (Benedikt *et al.*, 1973) indicated that it was composed of typical PE fibrillar material. In the present study the central disc is seen as an even layer of fibrils intermixed with ovoid bodies. TEM correlates of the ovoid bodies indicate that they consist not only of uveal pigment granules, as Davanger and Pederson (1975) observed, but also of various membrane-bound organelles and cell fragments. Their origin from iris pigment epithelial cells is deduced from the appearance of individual

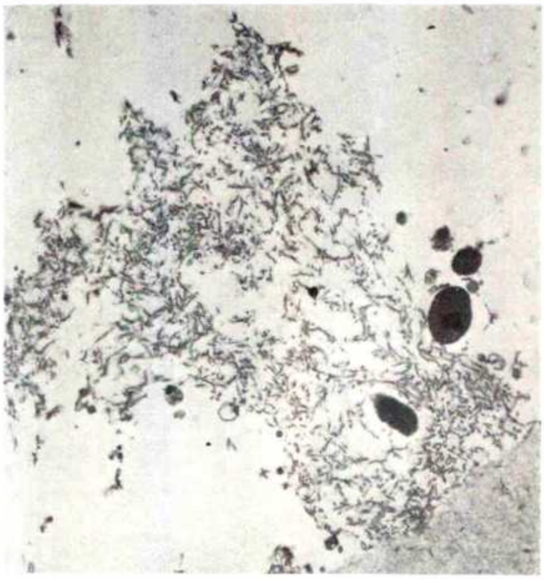

Fig. 7*a* *A vegetation of the granular zone showing admixture of fibrils and organelles.* *TEM* × 9530

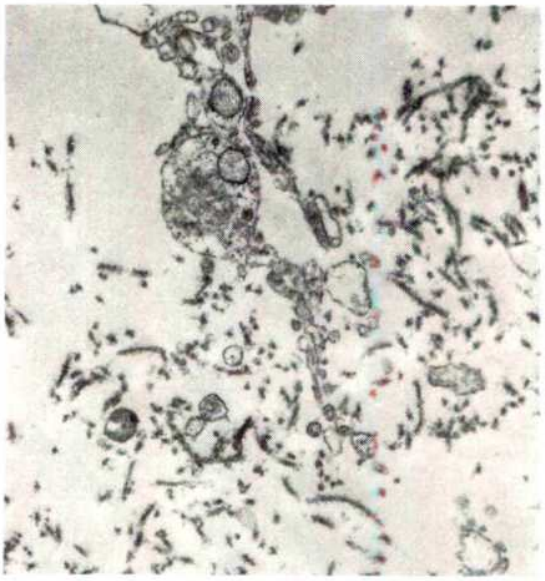

Fig. 7*b* *Detail from Fig.* 7a. *Cell remnants including organelles lie scattered randomly throughout the vegetation.* *TEM* × 18 518

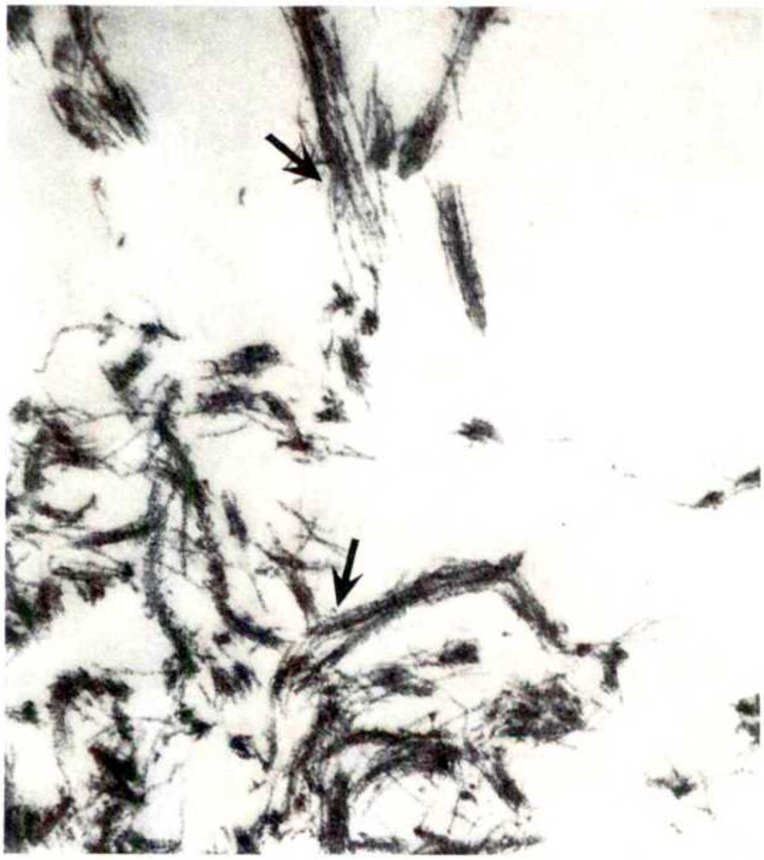

Fig. 8 *PE fibrils (composed of filamentous subunits* (arrows)*).* *TEM* × 56 130

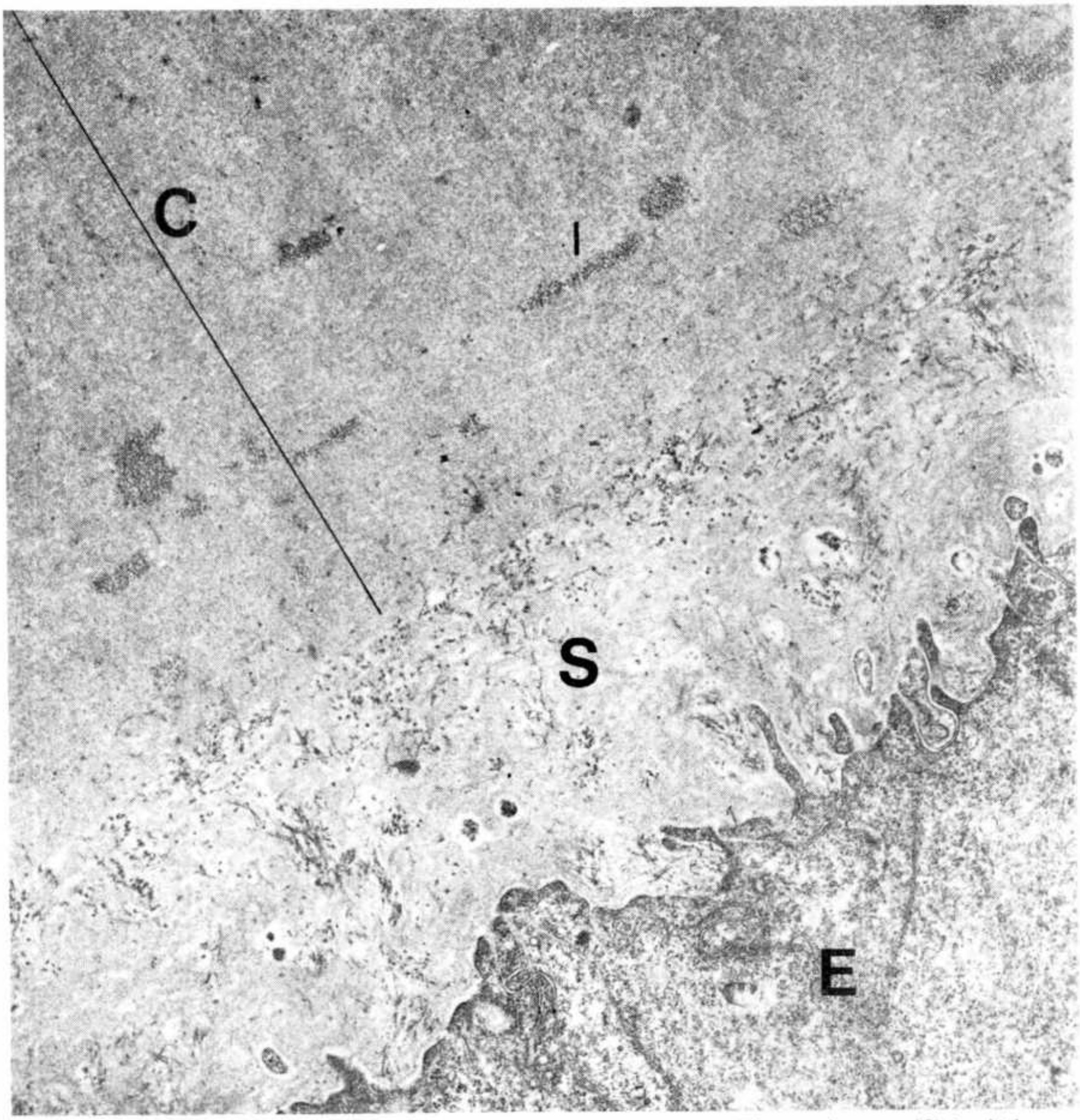

Fig. 9 *Pre-equatorial zone in PE disease. Capsule showing bilaminar structure. The capsule proper* (C) *in which are embedded numerous large granular inclusions* (I). *In the deep or striated portion* (S) *vertically orientated bundles of fibrils lie in pits of the underlying epithelial cells* (E) *many of which exhibit finger-like cytoplasmic processes. TEM* × 13 855

or even sheets of pigment cells which are strongly adherent to PE material on the pre-equatorial capsule. In some patients this bonding is so strong that lens delivery normally accomplished with surgical ease in this condition is possible only after overcoming protracted resistance.

The present study indicates that vegetations of the granular zone are also composed of the same elements—fibrils and organelles. There is poor correlation of fibril size when TEM and SEM measurements are compared. Our SEM measurements indicated a diameter of 40 to 60 nm. It is also certain that these measurements are exaggerated by carbon and gold coating. Davanger and Pederson (1975) observed that PE fibrils on the lens are coated with a layer of ruthenium red reactive material,

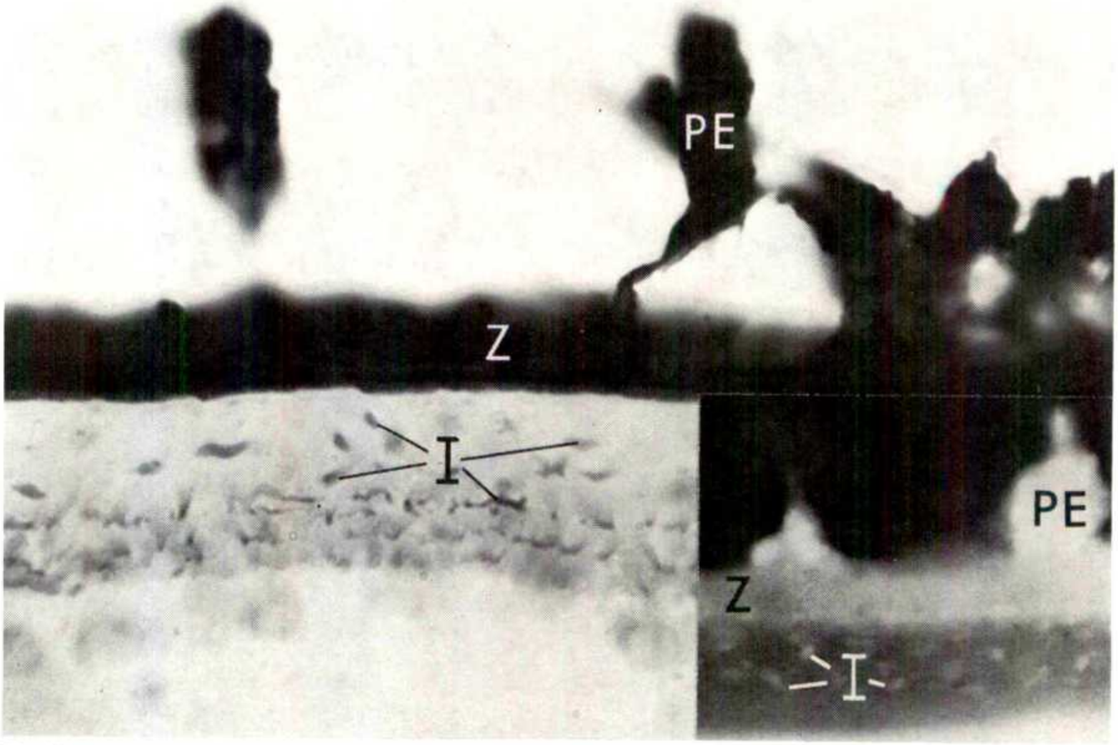

Fig. 10 *Pre-equatorial lens capsule. PE material* (PE) *on the lens capsule, the zonules* (Z), *and the capsular inclusions* (I) *are coloured blue-black. Chrome haematoxylin* × 1120. Inset *pre-equatorial zone showing green fluorescence of PE material* (PE) *on the lens surface and capsular inclusions* (I). *Zonules* (Z) *are unstained. Thioflavin T* × 673

presumably mucopolysaccharide, which may further contribute to this discrepancy. PE fibrils seen on TEM were reported to be up to 1 μm long by Ashton *et al.* (1965), whereas those seen here in SEM may be as long as 3 μm. Dickson and Ramsay (1975) noted that the fibrils composing the vegetations were of a larger diameter (25 nm) than those found on the surface layer (15 nm). In the present study no significant difference was noted between the fibril diameter in these two situations. Spiral fibrils on the surface of vegetations noted in SEM by Davanger (1975) were not encountered in the present study.

In spite of the generally acknowledged clinical frequency of lens subluxation in PE disease, the zonules appeared for the most part normal in the present TEM study, though occasional foci of infiltrations with PE fibrils were found. Further study of the zonules in PE disease is clearly indicated, especially near their ciliary attachments, the site at which spontaneous rupture seems to occur preferentially, as noted by Bartholomew (1970).

The amino-acid profile of PE material deposited on the lens was analysed by Ringvold (1973b) and found to be similar to that of amyloid. PE fibrils are generally about four times thicker than those of amyloid, which are usually 10 nm wide. However, Ringvold and Husby (1973) have shown that PE fibrils found in the iris are composed of several subunits each about 10 nm wide; a similar observation has been made for PE fibrils on the lens capsule in the present study. Moreover, PE fibrils found in the striated band of the pre-equatorial capsule are all about 10 nm wide, an observation first made by Davanger (1975) and confirmed by us. On occasion amyloid fibrils also show lateral aggregation, forming fibres about 40 nm wide as illustrated by Cohen (1968). Davanger (1975) has observed that individual PE fibrils are coated with mucopolysaccharide and lie in a mucopolysaccharide matrix, also resembling amyloid in this respect. Ringvold and Husby (1973) demonstrated that PE fibrils in the iris stained positively with fluorescein-conjugated antibody raised against liver amyloid. They did not, as confirmed in

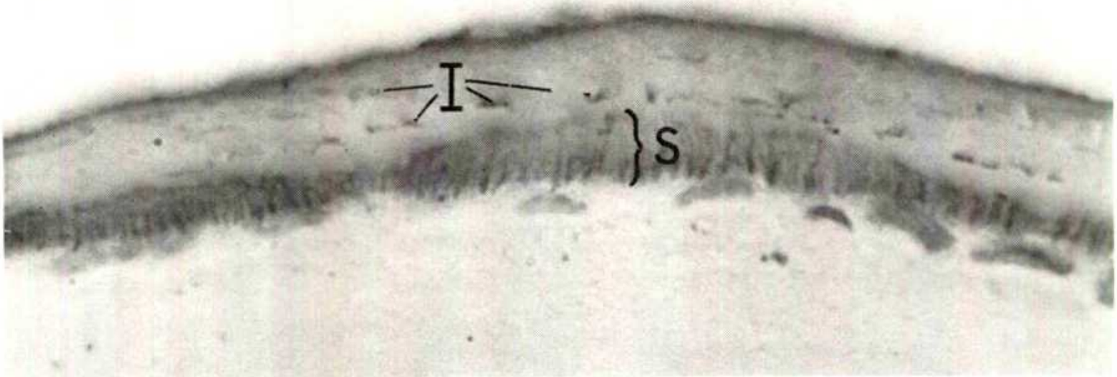

Fig. 11*a* *Pre-equatorial lens capsule in PE disease. Black vertical striae* (S) *in deep zone of capsule. Capsular inclusions* (I) *and zonules on the lens surfaces are also stained. Chrome haematoxylin* × 1108

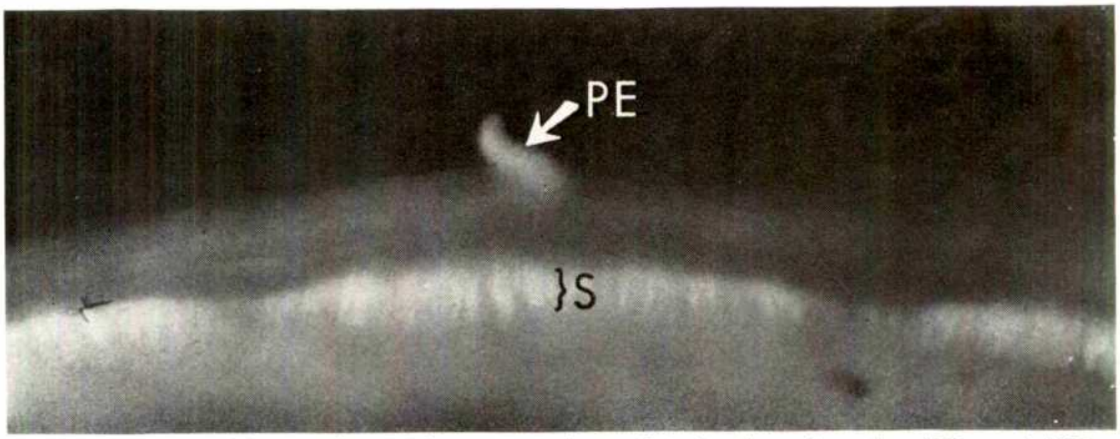

Fig. 11*b* *Pre-equatorial lens capsule in PE disease. Vertical striae* (S) *in deep layer of capsule and PE material* (PE) *on the lens surface show green fluorescence in ultraviolet light. Thioflavin T* × 1108

the present study, stain with fluorescein conjugates to lambda and kappa chains, so that it would seem unlikely that immunoglobulins are the source of PE fibrils. PE fibrils in the iris were shown by Ringvold and Husby (1973) to exhibit fluorescence in ultraviolet light after staining with the thioflavins T and S, we observed a similar reaction with PE fibrils on and in the lens capsule. It must be admitted, however, that thioflavin fluorescence, while typical of amyloid, lacks histochemical specificity.

Thus on the one hand PE and amyloid fibrils share a number of ultrastructural, biochemical, and histochemical properties. On the other hand, Congo red dichroism, generally regarded as the most critical histochemical test for amyloid, is not shown by PE fibrils in the iris (Ringvold, 1973b) or as note here in relation to the anterior lens capsule.

Glenner *et al.* (1972) consider amyloid to result from enzymatic (lysozomal) fragmentation of long-chain proteins (often immunoglobulins) into polypeptides, which polymerise spontaneously into an antiparallel beta-pleated sheet configuration, of which Congo red dichroism is probably the histochemical counterpart. They have thus founded the concept that under certain conditions, a pathogenic protein can be formed by proteolysis of an innocuous precursor. On the basis of the histochemical and electron microscopic findings in the present study of PE disease it may be suggested that the pre-equatorial epithelial cells synthesise long-chain zonule-like proteins, which are then converted by lysozomal enzymes (perhaps derived from the damaged or dying iris pigment epithelium) into small molecules capable of polymerising both within the capsule and in relation to nearby aqueous-bathed structures.

Peeling or exfoliation of the surface capsule in PE disease is not readily explained from the information available. The numerous organelles scattered over the anterior lens capsule in PE disease suggest that lysozomal enzymes could also play a role in exfoliation.

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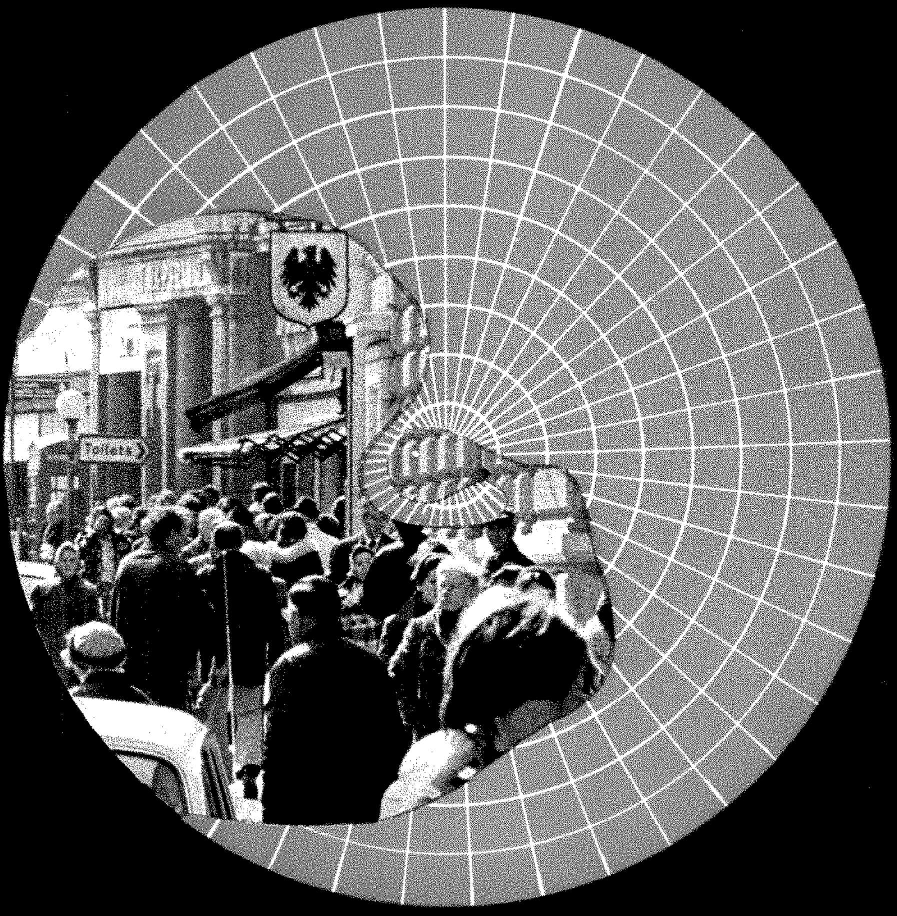

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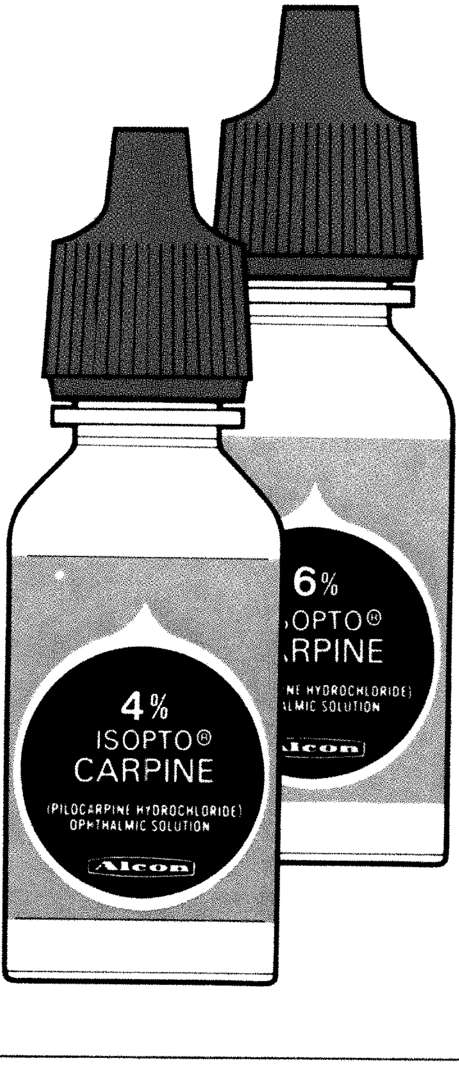

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Pseudoexfoliation of the lens in Australian Aborigines

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SUMMARY The first cases of pseudoexfoliation of the lens to be found in Australian Aborigines are reported. The prevalence rate in the communities in central Australia is 1·3% and for those 61 years and older is 16·3%. Within the limits of our assessment glaucoma was an associated finding in 8·1% of these cases. A high incidence of old trachoma, previous trauma, and Labrador keratopathy was also noted in these people.

Pseudoexfoliation of the lens (PXF) is a degenerative ocular condition, characterised by the deposition of a fluffy white material on the anterior lens capsule and on the surfaces of the anterior chamber, especially the pupil margin. It is often associated with the dispersion of pigment granules on the corneal endothelium and the trabecular meshwork, and with chronic open-angle glaucoma.

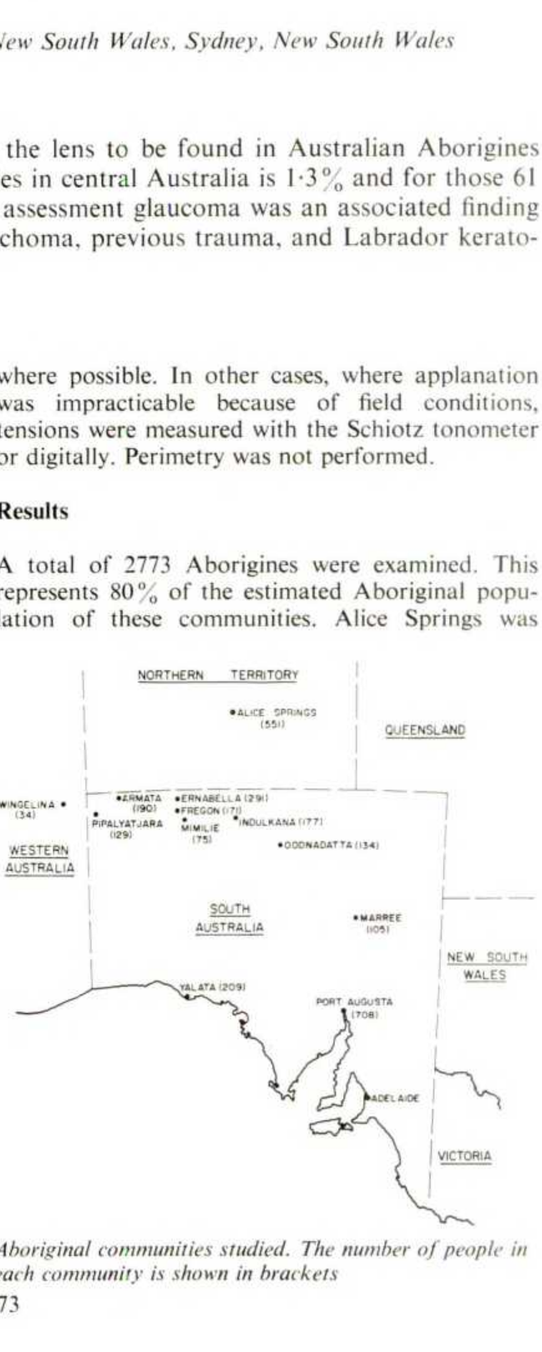
The incidence of PXF has been found to vary greatly in different races and different geographical areas (Duke-Elder, 1969; Aasved, 1969). This paper reports the first documented cases of PXF among Australian Aborigines, and presents the prevalence rate for this condition as it occurs in central Australia. The patients were identified during examinations undertaken by the National Trachoma and Eye Health Programme, which is assessing the ocular status of Aboriginal communities.

Materials and methods

A routine ocular examination under field conditions was performed on most members of Aboriginal communities in northern South Australia (see map). Visual acuity was assessed, and anterior segment examination for trachoma grading was made, using a × 3 loupe. If ocular disease was identified, the patient was examined on the slit lamp and ophthalmoscopy was done. Intraocular tension was measured by Goldmann applanation tonometry where possible. In other cases, where applanation was impracticable because of field conditions, tensions were measured with the Schiotz tonometer or digitally. Perimetry was not performed.

Results

A total of 2773 Aborigines were examined. This represents 80% of the estimated Aboriginal population of these communities. Alice Springs was



Aboriginal communities studied. The number of people in each community is shown in brackets

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excluded; only an initial survey has been undertaken there comprising 40% of the Aboriginal population. All cases were from members of the Pitjantatjara or related tribes; and all, except 2 cases, were thought to be full-blood Aborigines.

Clinical details of 37 cases of PXF are shown in Table 1. The distribution of PXF according to age is shown in Table 2. Pseudoexfoliation was not found in any person under 30 years old.

Every patient showed stigmata of trachoma, usually manifested as a superior corneal pannus. Nine people had Labrador keratopathy; 6 phthisical eyes were found; and in 1 case an eye had been enucleated. Three patients had had a unilateral cataract extraction; in 1 of these spontaneous resorption of the lens had occurred in the fellow eye. One case showed lens-induced uveitis. The rest of the patients, with the exception of 7 cases, had moderate to dense nuclear or cortical lens opacities in each eye.

Three cases (Nos. 24, 30, and 32) showed evidence of glaucoma; 1 case (No. 25) had elevated IOP, but the discs were not visible; and 2 cases (Nos. 19 and 28) had abnormally cupped discs and normal tensions.

Discussion

This is the first report of PXF in the distinct racial group of Australian Aborigines. Of the 2773 people examined 184 were over 60 years old. This gives a prevalence rate of 16·3% in this age group of 61 years upwards. The prevalence rates for younger age groups are 0·4% for 31 to 40 years, 1·6% for 41 to 50 years, and 2·8% for 51 to 60 years, no PXF being found in patients of less than 30 years.

Table 1 *Summary of clinical findings in 37 cases of pseudoexfoliation found in Australian Aborigines*

Clinical finding	*Number of cases*	*Percentage*
Raised IOP* with normal disc	1	2·7
Raised IOP with abnormal disc	3	8·1
Normal IOP with abnormal disc	2	5·0
Lens opacities	30	81·0
Dislocated lens	6	16·0
Labrador keratopathy	9	24·0

*IOP = intraocular pressure.

Table 2 *Distribution of PXF in Aborigines according to age*

Age in years	*Total examined*	*Total with PXF*	*Percentage with PXF*
0–30	2044	0	0
31–40	246	1	0·4
41–50	193	3	1·6
51–60	106	3	2·8
61+	184	30	16·3
Total	2773	37	1·3

These figures are interesting when they are compared with other prevalence figures in the literature. Luntz (1972) reported cases of PXF from the glaucoma unit in Johannesburg, South Africa, which showed an extrapolated prevalence rate of 0·001% in the White community, and 0·006% for the Bantu community. This was interesting, for, as he points out, other authors (Grable and Sugar, 1947) have considered PXF to be rare in American Negroes, who share a common gene pool with the Bantu. Our figures are most striking as we find an overall prevalence in the community of 1·3%, which is 300 times the prevalence found in the Bantu. Moreover, our figures are based on the examination of 80% of most communities and are not extrapolated from a glaucoma clinic population.

The prevalence in the over-60 age group is 16·3%. This is more than three times that found by Aasved (1969) in an examination of 2058 cases of the same age group from the cities of Bergen, Birmingham, and Bonn. His overall prevalence of PXF was 5·0%.

Glaucoma was found in association with PXF infrequently. Although we were limited in our ability to perform a full examination for glaucoma (in particular the lack of visual field testing), elevated intraocular pressure and pathological disc cupping was found in 3 cases. One case of unilateral ocular hypertension was found. This occurred in the affected eye of a patient with unilateral PXF. Two patients, with large optic discs (disc ratios in No. 19 of 0·4, 0·4; and in No. 28 of 0·3, not visible) and relatively low intraocular pressures (in No. 19 of 17, 17 mmHg; and in No. 28 of 20, 20 mmHg) were seen. In 1 (No. 19) the PXF and abnormal cupping were bilateral; the other case (No. 28) had unilateral PXF with abnormal cupping in the affected eye, the other disc could not be seen because of lens opacities. At present the distribution of ocular pressure in Australian Aborigines is not known. When this distribution is known, the pressures recorded in these cases may prove to be significantly raised. Thus the prevalence rate of raised intraocular pressure in PXF-affected eyes was 10·1% and of glaucoma of 8·1%. Luntz (1972) reported raised IOP in 79% of Bantu with PXF and 50% of Whites. In a study of the Norwegian population Aasved (1971) assessed the risk of eyes with PXF developing glaucoma as 20 to 25%.

In each case of raised pressure, the drainage angles were open on gonioscopy. As yet, no cases of chronic simple open-angle glaucoma have been reported in Australian Aborigines.

Pseudoexfoliation was found to occur predominantly in older patients; however, the youngest patient was only 35 years old. The youngest reported patient was 31 (Horven and Hutchinson, 1967). As the exact age of many of the older patients was not known, no attempt has been made to calculate the average age of the group and compare it with that of other series. Only 10 of the 37 cases occurred in females. Duke-Elder (1969) and Aasved (1969) state that there is no appreciable sex preference, although others have found a preponderance of males (Luntz, 1972; Gradle and Sugar, 1947).

In 21 cases PXF occurred bilaterally. In 7 of the 16 unilateral cases the unaffected eye was either phthisical, showed gross corneal scarring, or had been enucleated. One of the remaining unilateral cases had well-formed Kruckenberg spindles in both eyes. Seven of these unilateral cases involved the right eye and only 2 involved the left. Luntz (1972) also reported a preponderance of unilateral cases involving the right eye. The significance of this is not known. It is of interest that cases 6 and 7 were brothers. Aasved (1969) has summarised the occasional familial occurrence of PXF. Pseudoexfoliation was commonly associated with cataracts. Thirty patients had moderate to dense cataracts. In 6 of these there was also subluxation or dislocation of the lens.

Every patient showed stigmata of trachoma to a greater or less degree, and in this regard they reflected the general findings in the communities. The findings related to the prevalence and severity of trachoma in Aboriginal communities will be the subject of later reports. A high incidence of post-traumatic sequelae is noted, and reflects that seen in others of the same age group. Labrador keratopathy was also a frequent finding, and is seen commonly in older Aborigines. It is thought to be the end result of chronic exposure to bright sunlight and an arid environment (McGuiness *et al.*, 1972).

It will be interesting to see if the similar extremely high incidence of PXF will be found in other Aboriginal groups as the survey progresses, or whether it reflects a condition confined to the Pitjantatjara. If it is an isolated phenomenon, it would add great weight to the theory of a genetic basis for PXF.

The authors wish to thank members of the National Trachoma and Eye Health Programme for their assistance, in particular, Dr W. E. Gillies; and to express their appreciation for the co-operation shown by members of the Aboriginal communities visited.

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Ocular ultrastructural study in a fetus with type II glycogenosis

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SUMMARY The general pathological and ocular studies in an aborted fetus with type II glycogenosis revealed the widespread lysosomal storage of glycogen. Obvious lesions are observed in the viscera, in the skeletal and ocular muscles, and in all ocular tissues except the pigment epithelium of the retina. Brain and heart are relatively spared. Conjunctival and skin biopsies have a diagnostic importance, since specific alterations are evident early in the course of the disease.

Type II glycogenosis, an autosomal recessive disorder, is characterised by a lack of α-1,4-glucosidase (acid maltase) (Hers, 1963) resulting in the lysosomal storage of glycogen in various tissues (Baudhuin *et al.*, 1964). The muscles are mainly involved, and their abnormal contractile functions explain the symptoms of hypotonia, respiratory insufficiency, cardiomegaly, and cardiac failure leading to death within the first 2 years of life in the classical infantile form (Pompe disease). Glycogen storage has also been demonstrated in the liver, the kidney, the skin, and the nervous system in these cases (Hers and de Barsy, 1973). Less severe phenotypes have been reported, with childhood and adult onset (Engel *et al.*, 1973).

The disorder can be detected in utero by the enzymatic study of cultured amniotic cells. Subsequent therapeutic abortion permitted the investigation of the early biochemical and histopathological changes (Hug *et al.*, 1973; Nadler and Messina, 1969; Schaub *et al.*, 1974).

Toussaint and Danis (1965) observed by light microscopy the widespread storage of glycogen in the eyes of an infant with Pompe disease. Ultrastructural changes of the ocular muscles have been studied by Smith and Reinecke (1972), but the ocular lesions have not, to our knowledge, been reported by electron microscopy.

The purpose of this paper is to describe the lysosomal storage of glycogen in most of the ocular tissues in an aborted fetus with acid maltase deficiency. The presence of abnormal glycogen deposits within the conjunctival cells is important for the diagnosis of the disease by conjunctival biopsy, which was demonstrated in an unrelated case.

Case reports

CASE 1

This female fetus resulted from the fourth pregnancy of unrelated parents. Their first child died at 2 days of age because of oesophageal atresia. Their second child, a boy, presented a type II glycogenosis with prolonged survival to the age of 4 years 4 months. Pathological and biochemical findings have been previously reported (Martin *et al.*, 1976). Their third pregnancy ended with a spontaneous abortion, but the fetus was biochemically unaffected, with normal α-1,4-glucosidase activity.

During the 15th week of the fourth gestation a diagnostic amniocentesis was performed. Alpha-1,4-glucosidase activity was reduced to 1% of the normal range in the cultured amniotic cells. At the parents' request a therapeutic abortion utilising prostaglandin was performed at 22 weeks of gestation.

CASE 2

This male infant, the first child of unrelated parents, was admitted to hospital at the age of 3½ months because of muscular weakness, respiratory insufficiency, and heart failure. The diagnosis of classical infantile Pompe disease was based on the clinical picture and on enzymatic, biochemical, and histopathological studies of a muscle biopsy (Dr de Barsy). A conjunctival biopsy was performed at the age of 4 months. At this time the eyes were clinically normal.

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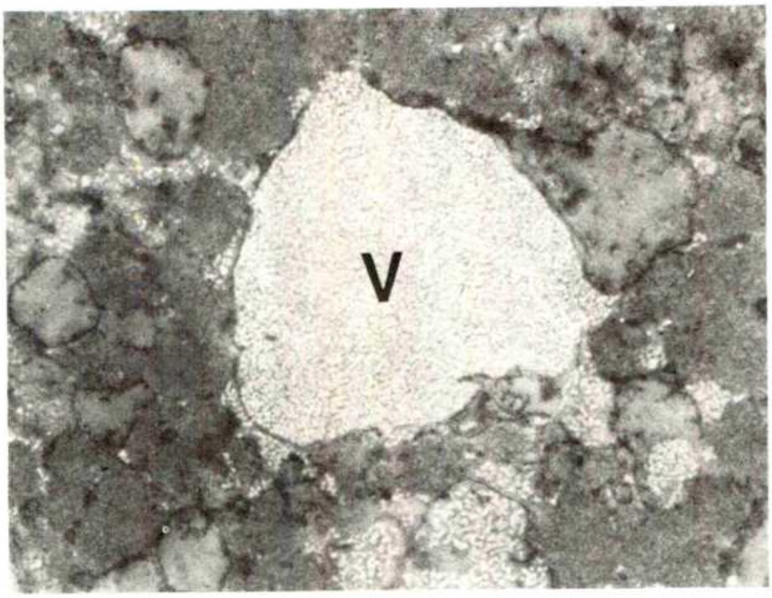

Fig. 1 *Biceps femoris muscle. A large membrane-bound glycogen vacuole (V) occupies the centre of a muscle fibre (uranyl acetate, lead citrate.* × 15 000)

Material and methods

The fetal tissues were obtained within 1 hour of abortion. The eyes, the nervous system, the visceral organs, and the skeletal muscles were fixed and processed for light and electron microscopy according to previously reported methods (Libert *et al.*, 1975; Martin *et al.*, 1973). The conjunctival biopsy of the second case was obtained under topical anaesthesia from the upper bulbar conjunctiva and prepared for electron microscopy by the same technique. After orientation of the specimens on semithin sections, ultrathin sections were cut with a diamond knife on a Reichert OmU 2 microtome, stained with uranyl acetate and lead citrate (Reynolds, 1963) or with silver proteinate after periodic acid oxidation (Thiéry, 1967), and observed with a Philips EM300 electron microscope. Compari-

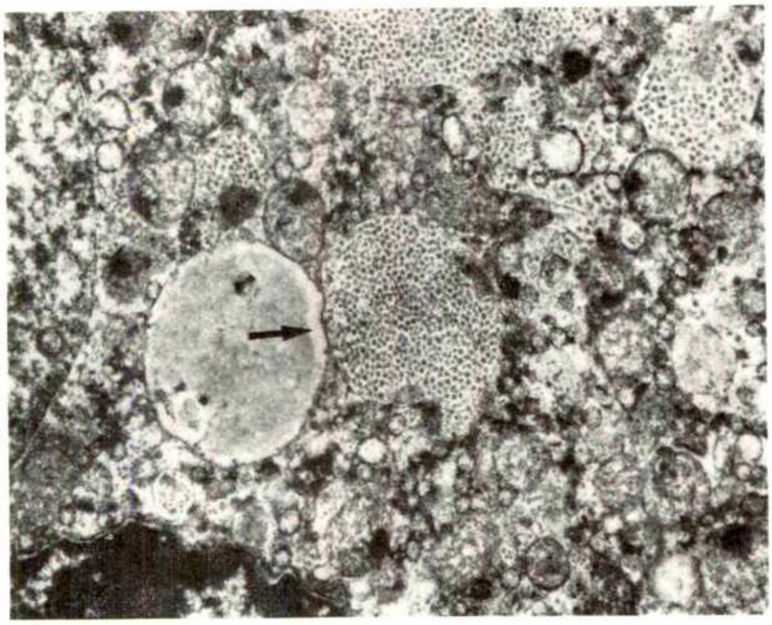

Fig. 2 *Liver. Numerous glycogen-filled vacuoles* (arrow) *are present in a hepatocyte (uranyl acetate, lead citrate.* × 15 000)

son was made with 3 normal fetuses aborted at similar gestation ages.

Results

AFFECTED FETUS

(*a*) General pathological examination (case 1): Lysosomal storage of glycogen was demonstrated both by histochemical and by ultrastructural methods in four different skeletal muscles (Fig. 1) (quadriceps, triceps suralis, biceps femoris, and biceps brachii), in the liver (Fig. 2), in the skin (fibroblasts, endothelial cells, Schwann cells), in the peripheral nerves (Schwann cells of myelinated and unmyelinated axons), and in the kidneys (distal convoluted tubules). The heart and central nervous system were relatively spared: a few glycogen inclusions were found in myocardial fibres and in neurons of the anterior horns and of the mesencephalic root of the trigeminal nerve. The other neuronal groups were devoid of any glycogen storage. Only the ganglion cells of the spinal ganglia were loaded with glycogen.

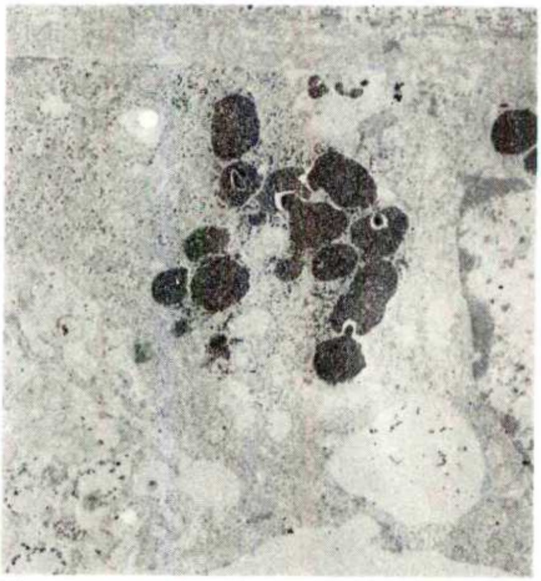

Fig. 3 *Cornea. The corneal endothelial cells contain free glycogen granules and storage lysosomes, which are markedly stained with silver (silver proteinate. × 10 000)*

(*b*) Ocular examination: Glycogen could be identified by light microscopy in the corneal epithelium and endothelium, in the lens epithelium, in the ciliary epithelium, and in the endothelium of the capillaries. The fetal retina seemed to be normal, though immature as in controls. The fibres of the oculomotor muscles contained many glycogen granules, but the general architecture was apparently conserved. These granules did not appear in salivary amylase-treated preparations.

In addition to confirming the lesions observed by light microscopy the ultrastructural studies demonstrated a more generalised storage process. Almost all examined cells displayed 0·2 to 1·5 μm membrane-bound inclusions, which contained innumerable small glycogen particles, moderately contrasted by routine techniques, and markedly stained by silver proteinate.

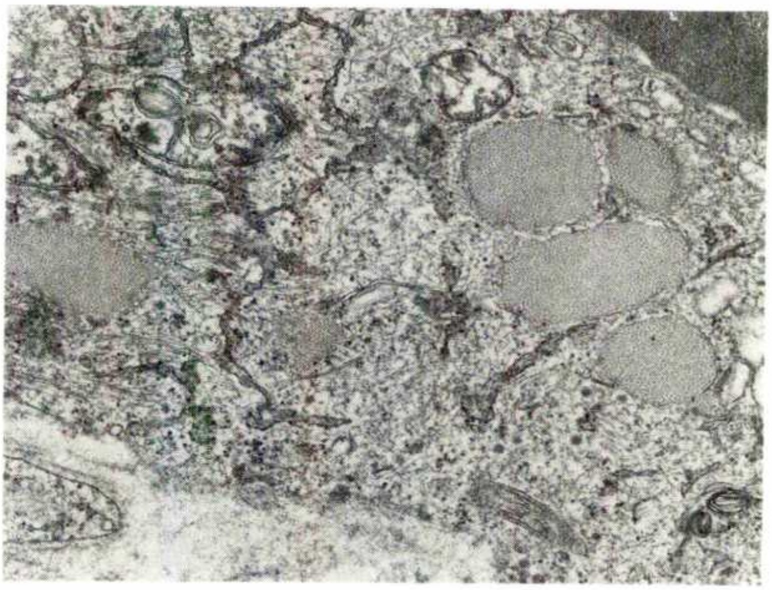

Fig. 4 *Choroid. Several glycogen engorged inclusions are evident in the endothelial cell of a choroidal capillary (uranyl acetate, lead citrate. × 22 000)*

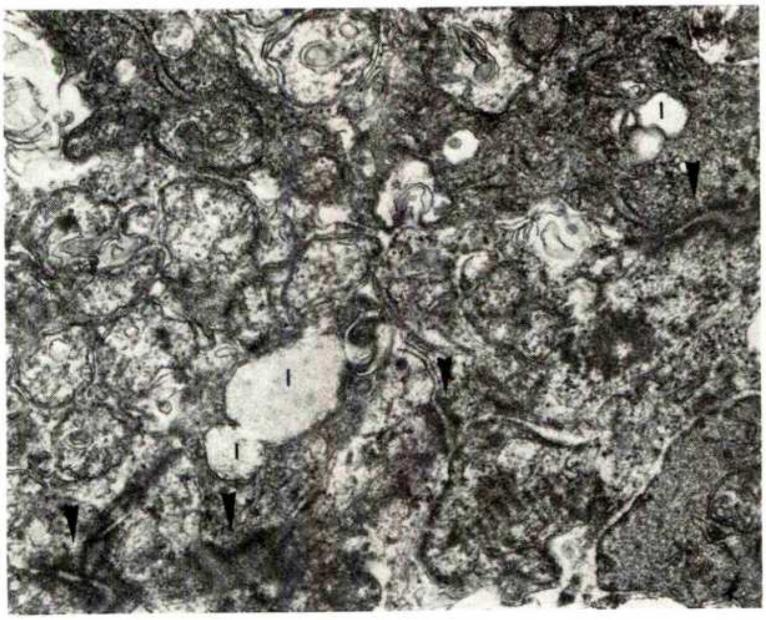

Fig. 5 *Retina. The immature photoreceptors contain some inclusions (I). The mitochondria are particularly numerous in this portion of the cell, near the external limiting membrane* (arrows) (*uranyl acetate, lead citrate.* × 25 000)

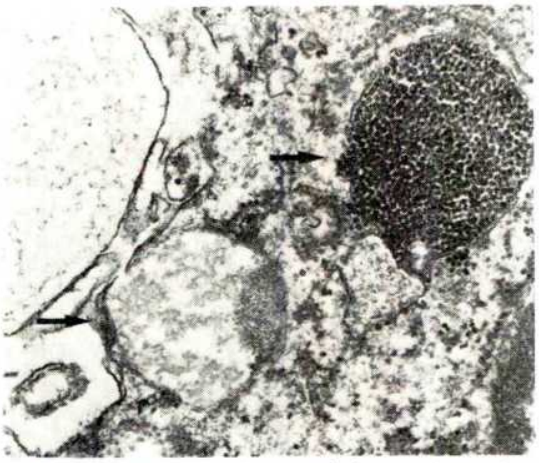

Fig. 6 *Optic nerve. The lysosomal glycogen* (arrows) *can be more or less contrasted by the routine staining technique in the same structure or even in the same cell, as in this glial cell* (*uranyl acetate, lead citrate.* × 34 000)

These inclusions were observed in the conjunctival and corneal epithelial cells, in the keratocytes, the sclerocytes, the corneal endothelial cells (Fig. 3), the fibroblasts of the conjunctiva, iris, and the choroid, in the capillary endothelial cells of the conjunctiva, the uvea, and the retina (Fig. 4), in the ganglion cells, the Müller cells, and the photoreceptors (Fig. 5). The glial cells of the optic nerve were also involved (Fig. 6). In contrast, the retinal pigment epithelium was unaffected.

The fibres of the extrinsic ocular muscles contained a variable number of storage inclusions. They were sometimes packed closely together and displayed a marked tendency to confluence (Fig. 7). Their dimensions varied from 0·2 to 5 μm. Some fibres were much disorganised, stuffed with membrane-bound vacuoles and large areas of apparently free glycogen deposits in which disrupted membrane residues were recognisable.

CONTROL FETUS

Isolated glycogen granules were observed in the ocular fetal cells. These particles were particularly numerous in the corneal endothelium, but they were lying free in the cytoplasm and never included within a unit membrane.

CONJUNCTIVAL BIOPSY

In the conjunctival biopsy of case 2 at 4 months of age the glycogen inclusions had the same ultrastructural aspect and dimension as in the fetal eyes, but they were much more numerous. The epithelial cells, the fibroblasts (Fig. 8), and the blood capillary endothelial cells were considerably distended by the storage vacuoles. The Schwann cells of the sensory nerves were also involved, while the axons and the myelin sheaths were normal.

Discussion

Alpha-1,4-glucosidase deficiency was demonstrated on cultured amniotic cells of a high-risk pregnancy

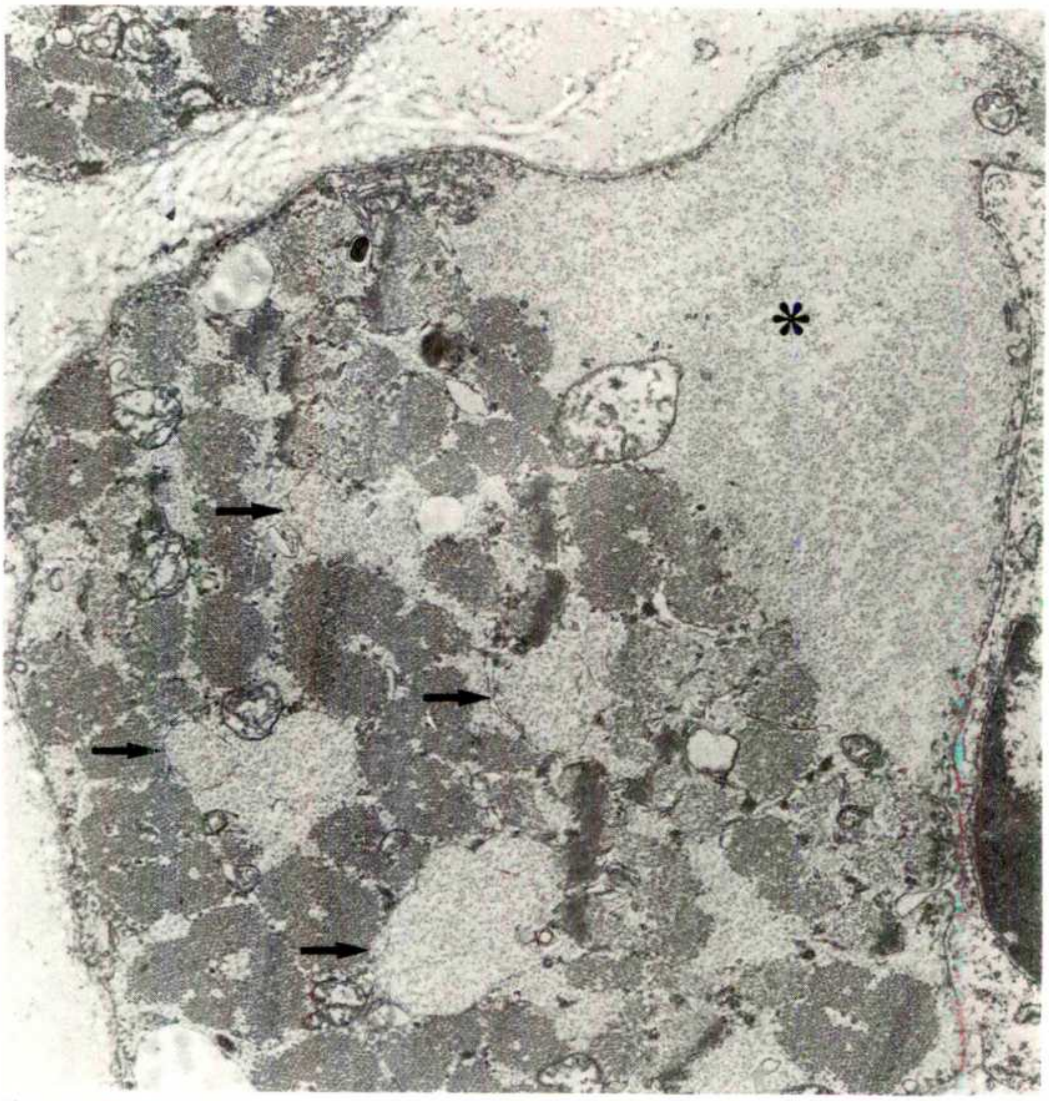

Fig. 7 *Ocular muscles. The lysosomes* (arrows) *show a marked tendency to confluence and sometimes occupy large areas of the cytoplasm* (asterisk) (*uranyl acetate, lead citrate.* × 16 000)

and resulted in the therapeutic abortion of a fetus with type II glycogenosis. This biochemical technique is now widely used for the prenatal diagnosis of lysosomal diseases and allowed histopathological and biochemical analysis of affected fetal tissues (Adachi *et al.*, 1974; Schneider *et al.*, 1972), including the eyes (Howes *et al.*, 1975). In our case these investigations indicated the early lysosomal storage of glycogen in skeletal muscles, liver, Schwann cells of peripheral nerves, skin, kidney, and to a much less extent in heart and central nervous system, strictly paralleling, although at a much earlier age, our previous findings in the affected sibling thought to represent a childhood phenotype rather than a classical example of Pompe disease (Martin *et al.*, 1976). It can be hypothesised that the relative sparing of heart and central nervous system accounted for the prolonged survival of the index case.

Although no ocular abnormalities except strabismus (Smith and Reinecke, 1972) have been reported clinically, the eyes are markedly involved in type II glycogenosis. Toussaint and Danis (1965) demonstrated on necropsy material the accumulation of glycogen in the mural cells of the retinal capillaries,

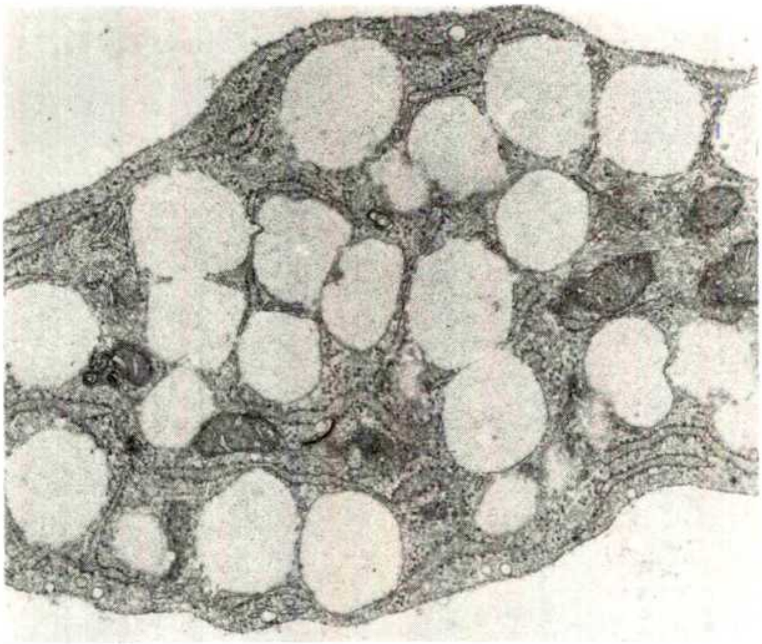

Fig. 8 *Conjunctiva. The fibroblasts of this conjunctival biopsy of case 2 display numerous and characteristic glycogen-engorged inclusions (uranyl acetate, lead citrate. × 28 000)*

in the ganglion cells, and in the smooth and striated muscle fibres of the eyes. Our light microscopic studies of an aborted fetus also suggest a widespread storage process. However, this might be a false conclusion because the fetal eye tissues are physiologically rich in glycogen, as shown in the controls.

Electron microscopy demonstrates clearly the generalised lesions. All ocular cell types, except the pigment epithelium of the retina, display membrane-bound inclusions which contain innumerable granules packed close together. The ultrastructural aspect of the inclusions and their staining properties with silver proteinate are characteristic of glycogen-engorged lysosomes, while the glycogen particles of the control fetal cells lie free and disseminated in the cytoplasm, and the lysosomes have the normal appearance of very small dense bodies.

The storage is much more important in the oculomotor muscles, in which the inclusions reach enormous size and sometimes disorganise the general architecture of the cells. Extensive areas of free glycogen particles containing residual membrane fragments suggest mechanical rupture of the distended lysosomes. However, it seems impossible to determine whether it was the result of an ante- or post-mortem process. These findings are consistent with ultrastructural studies on muscle biopsy and necropsy specimens in the brother of the present case (Martin *et al.*, 1976) and in other reported patients (Engel *et al.*, 1973; Martin *et al.*, 1973).

Smith and Reinecke (1972) examined by electron microscopy the inferior oblique muscle of a patient with type II glycogenosis. The tissues appeared less severely involved with deposits of free glycogen in generally well preserved muscle fibres, but the case seemed to belong to a milder clinical phenotype.

In case 2 the presence of many glycogen-engorged lysosomes in the conjunctival epithelial cells, fibroblasts, and capillary endothelial cells confirmed the diagnosis of type II glycogenosis by conjunctival biopsy. Skin biopsy also showed specific alterations in this disease (Martin *et al.*, 1976). These morphological diagnoses are certainly possible just after birth, as the tissues are already affected in the fetus.

Dr J. G. Leroy, head of the laboratory of medical genetics, Antwerp University Medical School, referred the fetus to us. He and Dr W. Den Tandt, in this laboratory, performed the enzymatic assays. We also thank Dr Vliers, Paediatric Cardiology, University of Louvain, and Dr de Barsy, I. C. P., University of Louvain, who permitted the conjunctival biopsy of case 2.

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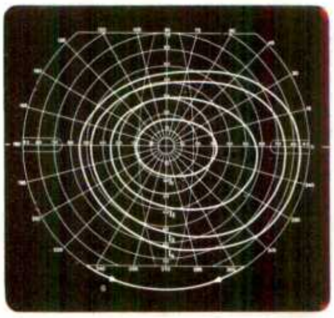

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British Journal of Ophthalmology, 1977, **61**, 483–488

Pulsating enophthalmos and choroidal hamartomas: two rare stigmata of neurofibromatosis

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SUMMARY A young girl with neurofibromatosis demonstrated two rare stigmata of this disease—pulsating enophthalmos and multiple pigmented choroidal hamartomata. Fundus photographs of the latter are believed to be the first of their kind to be published.

The ocular stigmata of neurofibromatosis, although inconstant and variable, should be familiar to ophthalmologists and other specialists likely to have to diagnose and treat the congenital hamartomatoses. Detailed reviews of the 'neurophakomatoses' are available and need not be elaborated here (Walsh and Hoyt, 1969; Vinken and Bruyn, 1972). We have recently seen a patient with neurofibromatosis who demonstrated two exceedingly rare stigmata of the disease—pulsating enophthalmos and choroidal hamartomata. The illustrations of the latter are, to the best of our knowledge, the first published photographs of these fundus lesions.

Case report

A 12-year-old right-handed White girl, examined in December 1970, was found to have neurofibromatosis. The right upper eyelid was diffusely thickened without a discrete mass, and the margin showed an S-shaped deformity (Fig. 1). Pulse-synchronous movement of the right globe was observed and exophthalmometry revealed 2–3 mm of right enophthalmos. The position of the globe could not be altered by head-hanging or Valsalva manoeuvre.

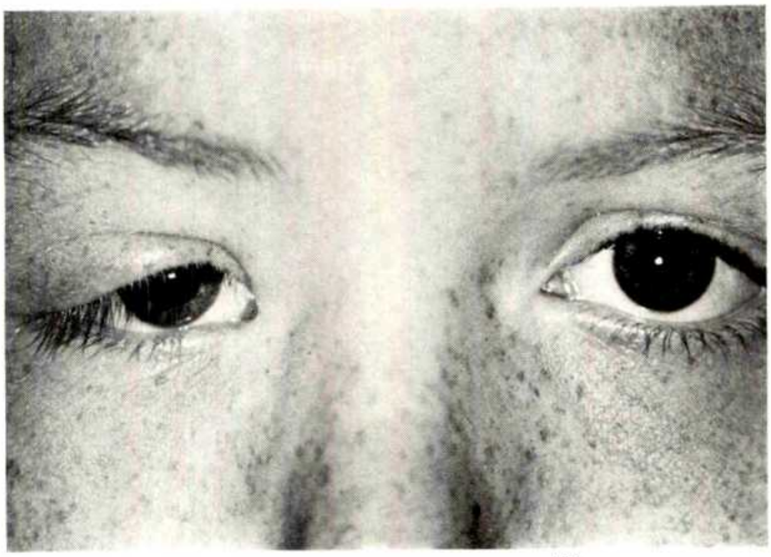

Fig. 1 *Note S-shaped deformity of right upper lid and enophthalmos of right globe*

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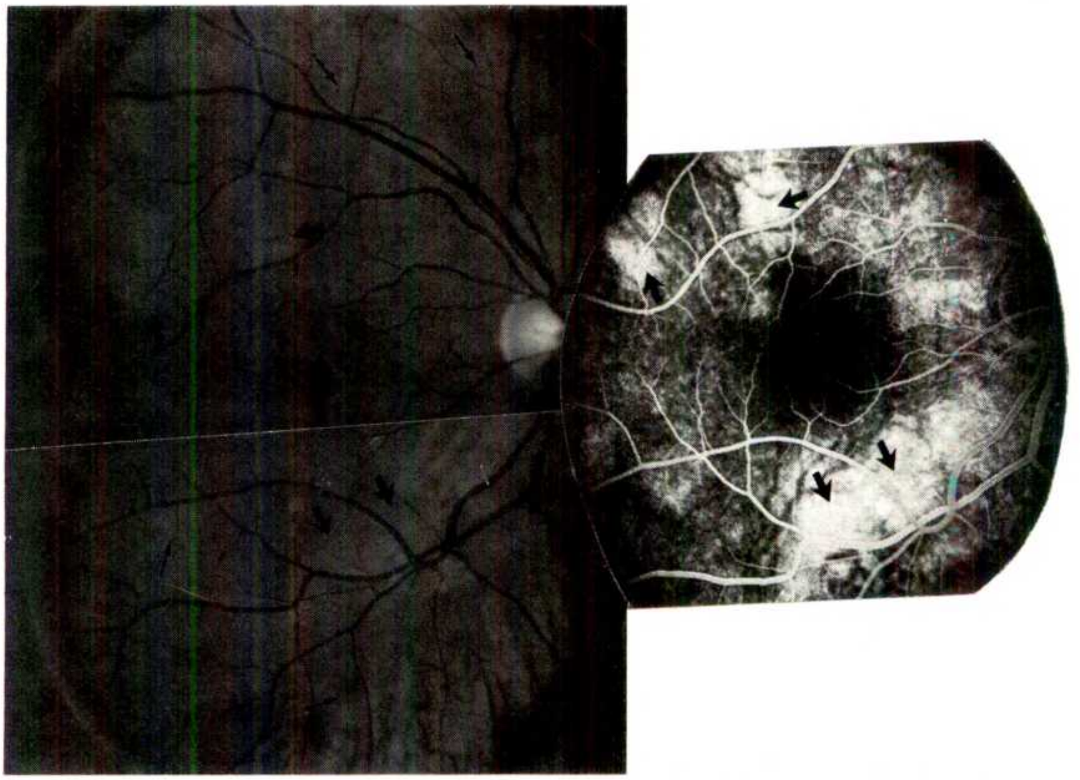

Fig. 2. *Fundus colour photographs show small, discrete hyperpigmented choroidal lesions* (small arrows) *associated with depigmentation of retinal pigment epithelium* (large arrows). *Black-and-white photograph of arteriovenous phase of fluorescein shows defect of retinal pigment epithelium filter over 'hyperfluorescent' choroidal lesions* (arrows). *Note that inferior lesion is more extensive than expected from colour photograph*

Best corrected vision was right 20/20, left 20/15 (RE: −4·50+2·00×80°; LE: −3·50+1·25×90°). Ocular motility, colour vision, pupillary responses and Goldmann perimetry were all normal. Slit-lamp examination showed two nodular iris lesions thought to be compatible with fibrous hamartomata.

Ophthalmoscopy showed multiple small, pigmented, circumscribed lesions along with larger hypopigmented areas (Fig. 2). Fluorescein angiography showed a pattern consistent with early choroidal filling defects and larger areas of hyperfluorescence during the arteriovenous phase. These findings were interpreted as areas of absent retinal pigment epithelium overlying variably pigmented hamartomata of the choroid, although histological confirmation was not possible.

Numerous large and small café-au-lait spots were scattered over the patient's body, and a large, raised violaceous fibroma molluscum was seen in the area of the left flank and abdomen. Neurological examination was normal.

Radiological examination of the skull (Fig. 3), including orbital tomography, showed enlargement of the sella with erection of the dorsum plus pronounced deformity of the greater and lesser wings of the sphenoid. The right optic canal and orbital fissure were grossly deformed and the right orbit expanded. These findings were thought to be consistent with sphenoidal dysplasia, an osseous malformation seen in neurofibromatosis.

Ocular, physical, and radiological re-examination in August 1973 showed no changes. Vision was at the same level and the right pulsating enophthalmos persisted. B-scan ultrasonography showed a defect of the right orbit, with no posterolateral wall echo and a suggestion of a temporally located smooth-walled mass.

Discussion

Neurofibromatosis is a heredofamilial disorder with multivariegated ocular and systemic stigmata.

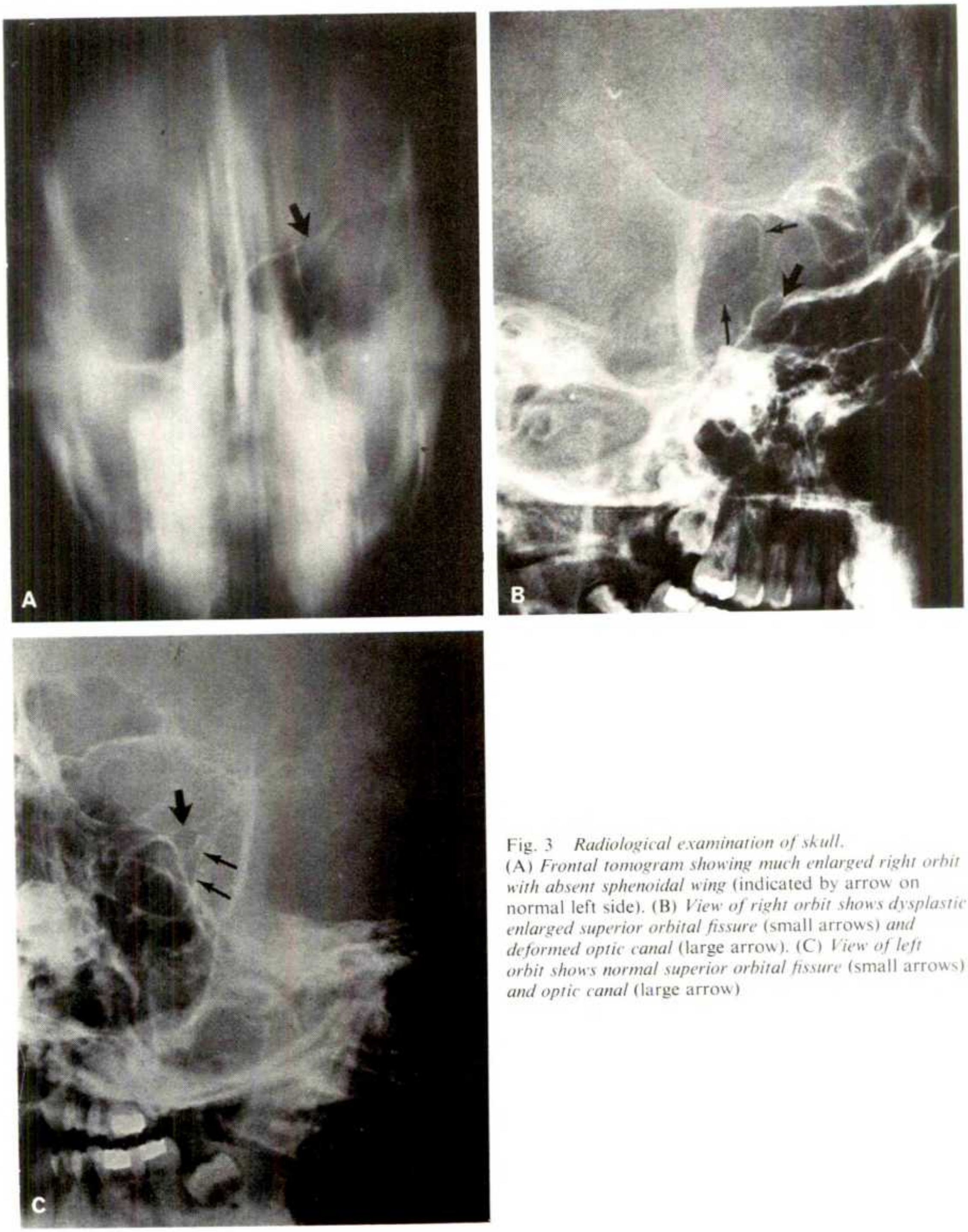

Fig. 3 *Radiological examination of skull.*
(A) *Frontal tomogram showing much enlarged right orbit with absent sphenoidal wing* (indicated by arrow on normal left side). (B) *View of right orbit shows dysplastic enlarged superior orbital fissure* (small arrows) *and deformed optic canal* (large arrow). (C) *View of left orbit shows normal superior orbital fissure* (small arrows) *and optic canal* (large arrow)

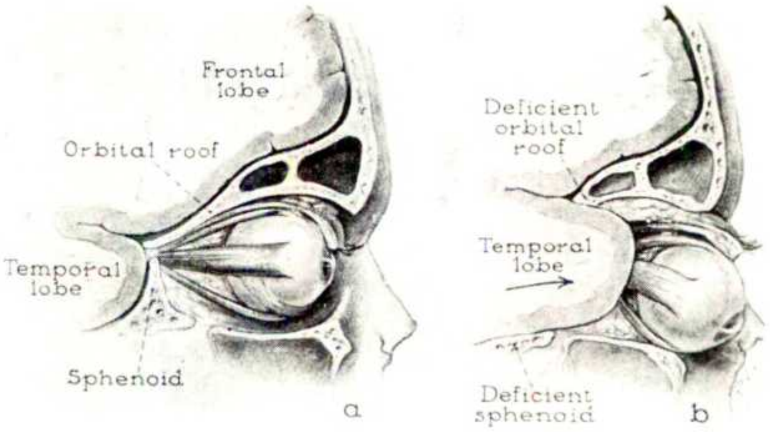

Fig. 4 *Diagrammatic representation of mechanism of pulsating exophthalmos in sphenoidal dysplasia* (Bruwer, A. J., and Kierland, R. R. (1955))

Exophthalmos, when present, is usually associated with a mass lesion in the orbit or a buphthalmic globe due to congenital glaucoma (Table 1). Exophthalmos accompanied by pulsating protrusion of the eye but without bruit indicates intracranial pulse waves transmitted to the orbital contents via a major congenital defect in the posterior wall of the orbit—a sphenoidal-orbital encephalocele (Fig. 4). Otherwise, pulsating exophthalmos is occasionally observed with few other lesions (Table 2).

Unilateral enophthalmos, on the other hand, is usually seen after orbital trauma as an early or late complication of orbital floor fracture. Other causes of unilateral enophthalmos must be considered quite rare (Table 3). The pulsating enophthalmos in our case was associated with a radiologically demonstrable sphenoidal dysplasia in a patient with other diagnostic stigmata of neurofibromatosis.

A review of the literature reveals only six potentially similar cases. Petres (1962) reported a case entitled 'Unilateral pulsating exophthalmos and neurofibromatosis'. In fact, the non-pulsating globe was exophthalmic by 4 mm, but 4·50 dioptres more myopic than the pulsating 'enophthalmic' globe. This patient underwent ipsilateral ligation of the carotid and jugular vessels with no relief of symptoms. Orbital *x*-rays were said to show enlargement of the optic foramen as the only radiological abnormality.

In his review of the orbital bony changes in neurofibromatosis Burrows (1963) reported the case of a 48-year-old woman (case 10) with a pulsating enophthalmos and a large ipsilateral defect of the sphenoid bone. Vision and ocular movements are described as 'good' without any further clinical details. Lenshoek *et al.* (1968) reported the case of a 15-year-old girl with pulsating enophthalmos accompanied by an audible murmur. An exophthalmic phase would appear during periods of emotion. Enlargement of the ipsilateral orbit with destruction of both sphenoid wings was demonstrable radiologically.

Nikiforov (1966) described the case of a 28-year-old man who during a physical exertion experienced the sudden onset of severe left-sided head pain, diplopia on right gaze, and rapidly progressing left pulsating exophthalmos, followed by loss of consciousness and a seizure. A 'blowing noise', which disappeared on ipsilateral carotid compression, was heard over the left supraorbital region. The deep tendon reflexes were increased on the right side

Table 1 *Causes of exophthalmos in neurofibromatosis*

(1) Orbital tumour
  (*a*) Neurilemoma
  (*b*) Plexiform neuroma
  (*c*) Meningioma
(2) Optic nerve glioma
(3) Nerve sheath meningioma
(4) Sphenoidal-orbital encephalocele
(5) Buphthalmos (congenital glaucoma)

Table 2 *Causes of pulsating exophthalmos*

(1) Carotid-cavernous fistula
(2) Sphenoidal-orbital encephalocele (dysplastic, traumatic or surgical)
(3) Orbital venous varix or arteriovenous malformation
(4) Vascular tumours (hemangioma)

Table 3 *Causes of enophthalmos*

(1) Orbital floor fracture
(2) Fat atrophy (traumatic)
(3) Facial hemiatrophy (scleroderma, *en coupe de sabre*)
(4) Sclerosing orbital tumour
(5) Microphthalmos or phthisis bulbi
(6) Orbital fibrosis

and there was a right positive Babinski sign. Left carotid arteriography showed an 'inferiorly displaced middle cerebral artery, a left orbital bony defect, but no aneurysm'. The left eye became 12 mm enophthalmic and later stabilised at 3 mm enophthalmos. The author speculates that the patient originally had had a longstanding left pulsating enophthalmos associated with neurofibromatosis and that the acute episode was due to herniation of the meninges and temporal lobe into the orbital defect. We believe this case was most likely one of carotid-cavernous fistula with late enophthalmos.

Dabezies and Walsh (1961) recorded the case of a 27-year-old man with pulsatile enophthalmos who, 10 years previously, had sustained left frontotemporal trauma of sufficient force to render him unconscious for three days. Orbital *x*-ray examination revealed bony defects of the sphenoidal wings and the orbital portion of the frontal bone, which was partially absent. The authors suggested that the enophthalmos was due to post-traumatic atrophy of orbital fat.

Finally, Vinken and Bruyn (1972) cite two cases of pulsating enophthalmos. The first (Kelly, 1949) concerns a patient with neurofibromatosis and a large parasellar mass in whom the presence of pulsating enophthalmos is mentioned cursorily with no further details. The second case is that of a patient reported by Franceschetti and Streiff (1938). However, review of the original article shows this to be a case of pulsating exophthalmos (*esoftalmo con pulsazione*) and not enophthalmos.

It would therefore seem that primary pulsating enophthalmos uncomplicated by trauma or other precipitating events is extremely rare.

In the present case the classical dysplastic defects in the sphenoid bone are sufficient to account for the pulsations, although the enophthalmic position of the globe cannot easily be explained. The radiographic appearance of this dysplasia has been described by Binet *et al.* (1969) in a study of seven patients thought to have neoplasms or chronic subdural haematomas. It is important to note that, in addition to hypoplasia of the greater sphenoid wing, a raised lesser wing, sellar deformities, and enlarged middle cranial fossa, in all patients the ipsilateral orbit was enlarged. In five patients with optic foramina views the optic canal was enlarged or 'destroyed', but only one patient had visual loss and was found to have an optic nerve glioma. Although the other patients were not surgically explored it was concluded that the abnormal optic foramina were due to the congenital sphenoidal dysplasia.

In our case B-scan ultrasonography showed an abnormality of the retro-orbital fat pad, which appeared less dense and smaller than in the normal orbit. This finding may account for the enophthalmos. Regarding the fundoscopic findings, choroidal lesions in neurofibromatosis are very rare, although it is said that melanoma occur more often in patients with neurofibromatosis (Table 4) (Font and Ferry, 1972).

Table 4 *Fundus findings in neurofibromatosis*

(1) Optic atrophy associated with optic nerve/chiasm glioma
(2) Gliomatous raising of optic disc
(3) Optic atrophy associated with hydrocephalus
(4) Glaucomatous cupping due to congenital buphthalmos
(5) Choroidal melanoma
(6) Choroidal naevi
(7) Multiple pigmented choroidal hamartomata
(8) ? True retinal glioma
(9) ? Increased incidence medullated nerve fibres

Nordmann and Brini (1970) suggest that the association of neurofibromatosis and pigmented tumours reflects a disturbance in the development of neural crest cells derived from neuroectoderm, which in turn give rise to Schwann cells, meningoblasts, and melanocytes of the skin and uvea—hence the increased incidence of schwannomas, meningiomas, and melanomas in patients with neurofibromatosis. These authors further point out that although nodules and benign melanomata of the anterior segment of the eye are very common in neurofibromatosis such lesions in the posterior pole are exceptional and 'almost certainly not related to the disease'. Included in this publication was a fundus photograph of a large choroidal naevus.

Commenting on such choroidal lesions, Wolter *et al.* (1962) state that when they do occur they are associated with a typical clinical picture of congenital unilateral glaucoma leading to buphthalmos and blindness. Microscopically the posterior choroid is diffusely thickened, containing many ganglion cells, nerve-fibre bundles, and lamellated 'ovoid bodies' made up of elongated hyperplastic Schwann cells. Wolter (1965) subsequently concluded that nerve fibres actually branch between the onion-like layers of these Schwann cells, thus resembling sensory nerve end-organs.

Although pathological confirmation was impossible, we believe that from the clinical appearance and fluorescein pattern of the choroidal lesions in our case they represented hamartomatous stigmata of neurofibromatosis. We do not know of any previously published fundus photographs.

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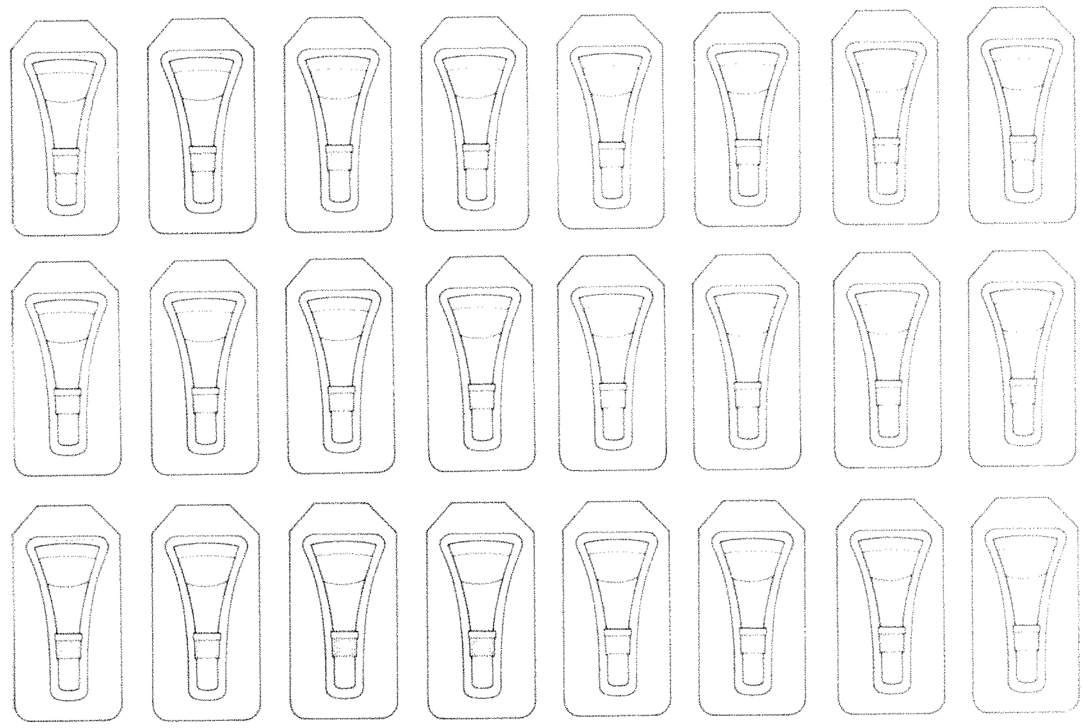

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British Journal of Ophthalmology, 1977, **61**, 489–493

The Elidice: new instrument for visual acuity self-screening

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SUMMARY A compact electronic device which enables the user to determine for himself whether his visual acuity reaches a chosen standard has been constructed at a cost of £25. The instrument provides a test which requires the observer to respond to the orientation of a sequence of red Landolt-Cs and which takes under five minutes to complete. 'Crowding' effects associated with conventional letter charts are avoided and the test does not discriminate against astigmatic observers. One hundred observers were tested on both the new instrument (the Elidice) and a standard Snellen chart under clinical conditions. The overall agreement between the two tests was 87·8%, with the Elidice having an over-referral level of 10·7% and an under-referral level of 1·5% as compared with the letter chart. This makes the Elidice particularly suitable for the regular screening of laser users for reduced visual acuity due to macular damage.

This paper describes a relatively simple, inexpensive instrument specifically designed to enable users of lasers to monitor their central visual acuity once their zero line has been established in a clinical examination. In general, it provides a self-screening test for checking whether visual acuity reaches a predetermined standard—as required, for example, in the British number-plate test which has to be passed by drivers of motor vehicles. Previous authors (Crossman *et al.*, 1970; Decker *et al.*, 1975) have described instruments for automatically measuring visual acuity. The earlier system requires a computer to control the test, and the mechanical complexity and high component count of the latter instrument make it expensive to produce. For testing to a predetermined standard a simpler instrument is desirable.

The test is based on the well-known Landolt-C (Landolt, 1899), which can be presented with its gap in one of several positions; recognition of the gap orientation implies that the 'C' can be resolved. This character provides a suitable test of central visual acuity (which is most likely to deteriorate with laser damage) and is simple to produce as a self-luminous target, so that it can be used under rigidly controlled conditions of illumination.

The instrument (Fig. 1) is called the Elidice (from an acronym for light-emitting diode C). The prototype was designed for 15 presentations of the target. A light on the response panel indicates whether the observer has passed the test (by 13 or more correct responses) or failed (by 3 or more incorrect responses). The probability of passing the test by pure guesswork is 0·00009%, as determined by the binomial distribution.

System description

The target consists of a circular array of 12 red diffused light-emitting diodes (LED) (Litronix RL-T1). During the test presentation eight LEDs providing the fixed segments are always illuminated. Three of the other four LEDs, providing the test segments—corresponding to top, bottom, left, and right in the array—are also illuminated, to produce the Landolt-C display. The blank test segment is chosen randomly.

Although it is possible to make this choice with a pseudorandom sequence generator, the requirements of a reasonable sequence length and a one-of-four output (rather than the usual binary code) would make for complex circuitry. Instead, a simpler system is used. An oscillator runs continuously between test presentations and its output is divided by a modulo-4 counter. The counter outputs are decoded by gates to select one of the four test segments. During the presentation the oscillator is

The development of the Elidice was supported by a Medical Research Council project grant to R.A.W. K.A. is in receipt of an MRC research studentship

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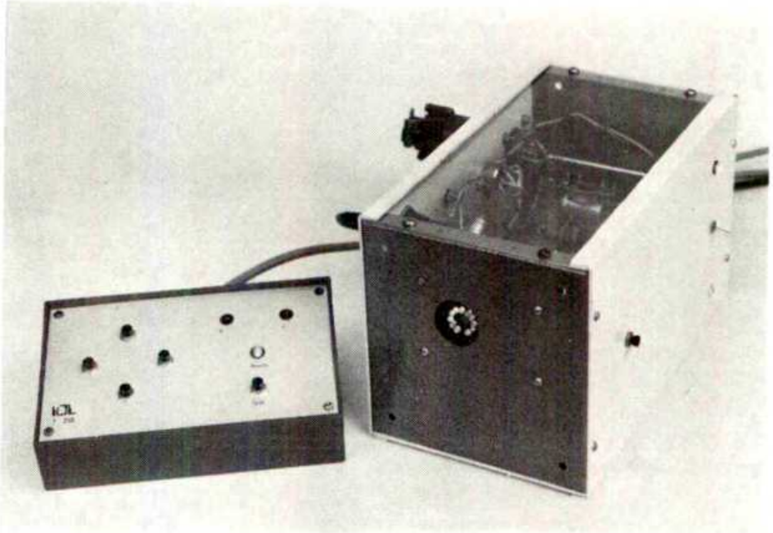

Fig. 1 *The Elidice, showing response panel (left) and LED target*

stopped to produce a stationary display. The test sequence is determined by the time intervals between successive presentations. By setting the oscillator frequency to about 10 kHz it is impossible for the observer to produce a predictable sequence.

A block diagram of the system is shown in Fig. 2. Initial conditions are established by pressing the 'reset' key. The master reset pulse clears the error and answer counters, resets the input and result latches, and illuminates the 'ready' indicator. Pressing the 'test' key sets the input latch, stops the oscillator, and resets the answer latch. The 'ready' indicator is extinguished and, after a short delay to allow the system to settle, the display monostable is triggered and illuminates the target.

If an 'answer' key is pressed the response is detected by the answer gate and entered in the answer latch. The answer is compared with the test segment signal and, if wrong, it is counted in the error counter. At the same time the answer counter is incremented and, after a short delay, the display monostable reset. This turns off the display, resets the input latch, turns on the 'ready' indicator, and starts the oscillator again. If there is no response from the observer the display monostable resets itself after about three seconds and the contents of the counters do not change. Spurious counts are avoided by accepting answers only while the display is on, and the 'check answer' comparison is accepted only when an answer key has been pressed.

If the error count exceeds two the result latch is set to 'fail'. When 15 responses have been recorded by the answer counter the input gate is disabled to stop the test and the 'pass' or 'fail' indicators are enabled to display the test result.

The prototype uses a total of 15 CMOS logic integrated circuits and is mounted in a 225 × 135 × 135 mm box, with a remote response panel carrying the 'test' and 'answer' keys and the 'pass', 'fail', and 'ready' indicators. The total component cost was about £25.

Clinical tests

The Elidice was evaluated in comparison with a standard Snellen letter chart internally illuminated with four 25-W light bulbs. The target LEDs were operated at a current of 10 mA, giving a typical luminance of 0·4 mcd at 650 nm. All the clinical tests were performed with a background illumination of 0·1 lux in the refraction clinic of Moorfields Eye Hospital as an extension to, and under the same lighting conditions as, the refraction examination. One hundred volunteer staff and patients comprising 42 males and 58 females served as observers. The total age range was 9 to 86 years, with 55 observers under, and 45 over, 40 years of age. The tests were conducted under monocular conditions with the fellow eye occluded, and to obtain additional data some persons were tested without their usual lens corrections. This brought the total number of tests to 205.

Viewing distances of 6 and 10 m were used with the Snellen chart and the Elidice respectively. At 10 m the gap in the 'C' subtends the same angle at the eye as the critical dimension of the letters on the 1·0 (6/6) line of the letter chart—that is, one minute of arc. Thus a person with 1·0 acuity or better, as measured by the Snellen test, should pass on the Elidice, whereas one with an acuity of 0·67

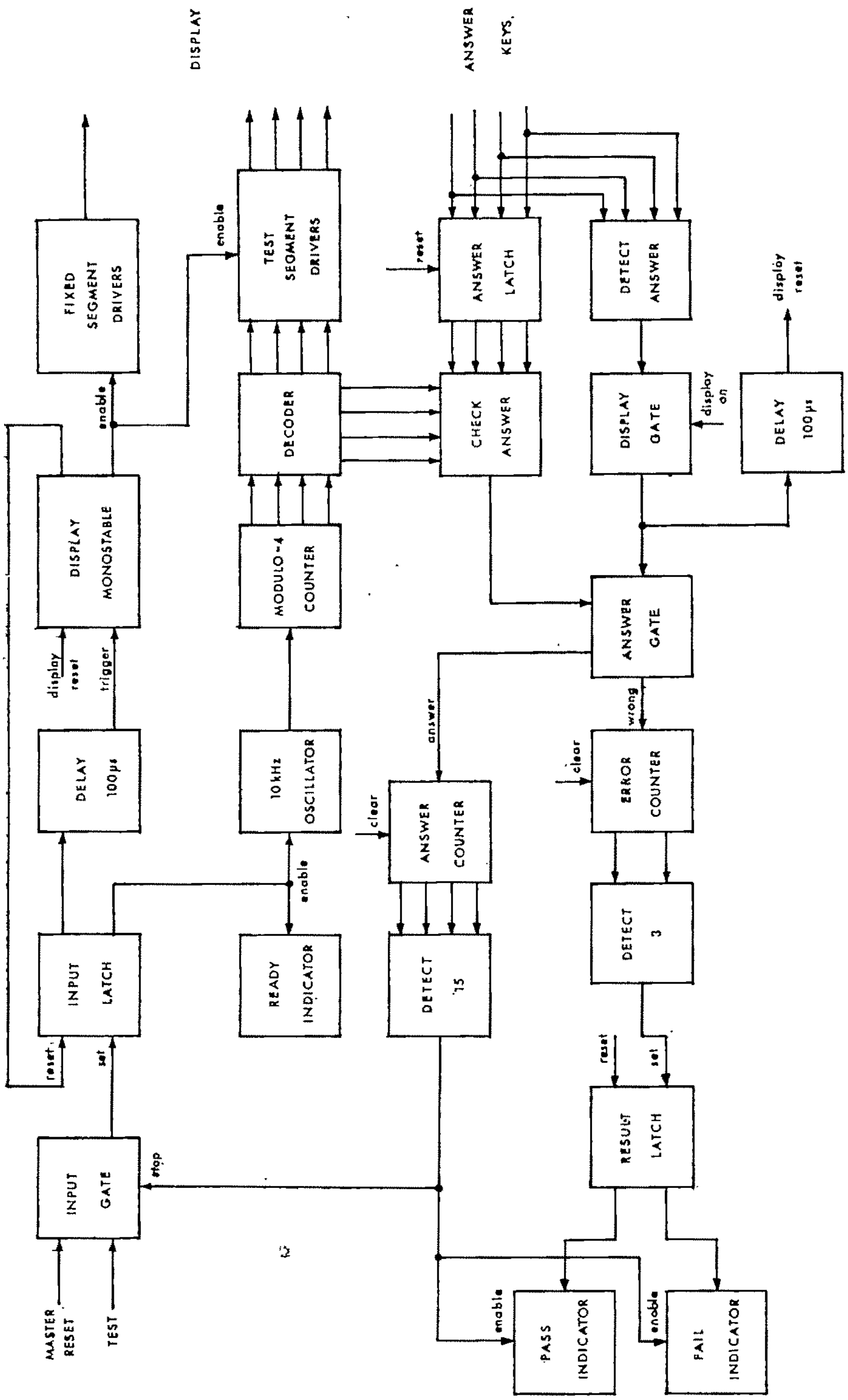

Fig. 2 *Block diagram of the Elidice system*

(6/9) or worse should fail. The instrument agreement is defined as the percentage of evaluations which satisfy these criteria.

Results

The overall instrument agreement between the Elidice and the Snellen chart was 87·8%, with the new test having an over-referral level of 10·7% and an under-referral level of 1·5% when compared with the Snellen chart. The percentage of eyes passing the Elidice test as a function of their Snellen acuity is given in Table 1 together with corresponding χ^2 values comparing the number of eyes passing on the Elidice with the number failing the test. At all levels of acuity the probability of there being no correlation between an observer's performance in the Elidice test and his performance in the Snellen letter test was smaller than 0·02.

Non-parametric statistical procedures (χ^2 test, Fisher exact probability test) were applied to the data to see if particular groups of observers (that is, males *v.* females, staff *v.* patients, under 40s *v.* over 40s) were preferentially passing or failing on the Elidice; χ^2 values (Table 2) suggest that men with acuities of 1·0 or better were more likely to pass the Elidice test than women with acuities of 1·0 or better ($P<0{\cdot}02$). Table 2 also indicates that patients with acuities less than 1·0 were more likely to fail on the Elidice than staff with the same acuities ($P<0{\cdot}01$). The remaining values of χ^2 presented in Table 2 are not significant at the 0·05 level. In all cases the Fisher exact probability test led to the same conclusions as the χ^2 tests.

Some of those observers with acuities of 1·0 or better were colour-defective or wore optical corrections greater than 4 dioptres. However, any difference in the ability of these groups to pass the Elidice test compared with colour-normals and those wearing corrections smaller than 4 dioptres is not significant at the 0·05 level (χ^2 comparing colour-normals with colour-defectives = 0·00045; $P<0{\cdot}99$; comparing larger optical corrections with smaller corrections = 1·27; $P<0{\cdot}3$).

Table 1 *Percentage of eyes passing on the Elidice as a function of their Snellen acuity*

Snellen acuity	*% passing on Elidice*	χ^2 *(DF = 1)*	*Significance (P)*
1·20	88·9	54·44	<0·001
1·00	70·0	6·40	<0·02
0·67	5·4	29·43	<0·001
0·50	0	11·00	<0·001
0·33	7·1*	10·29*	<0·01*
≤0·25	0	13·00	<0·001

* % passing is zero when 1 amblyopic eye is excluded ($\chi^2=14{\cdot}00$, $P<0{\cdot}001$). See text

Table 2 *Statistical evaluation of differences among observers in their ability to pass on the Elidice (DF = 1)*

Snellen acuity	*Male/female*		*Staff/patients*		*≤40/>40*	
	χ^2	*Significance (P)*	χ^2	*Significance (P)*	χ^2	*Significance (P)*
≥1·00	5·69	<0·02	1·66	<0·20	0·86	<0·50
<1·00	0·05	<0·90	7·49*	<0·01*	0·87	<0·50

* $\chi^2=0{\cdot}11$, $P<0{\cdot}80$ when 1 amblyopic eye is excluded (see text)

Discussion

Most observers had little difficulty in performing the test, which takes under five minutes to complete. The most common problem related to the need to look up at the target and then down at the response panel to record an answer. Some elderly patients were arthritic and could not always respond sufficiently quickly. These problems could be alleviated by lengthening the display time to perhaps 5 or 10 seconds and mounting the response panel in the same plane as the target. Clearly, however, an elementary level of manual dexterity is needed.

The clinical trials show that the Elidice is a slightly more severe test than the Snellen chart, but this is desirable in a screening test. The known superiority of men in visuo-spatial tasks (Coltheart *et al.*, 1975) is reflected in the data for observers with good acuity. The Elidice requires the observer to respond manually as opposed to verbally in the case of the Snellen chart. For observers with poor acuity (less than 1·0) the data indicate that staff are more likely to pass on the Elidice than patients. Of the six staff eyes with poor acuity, however, one was amblyopic and could read letters at the beginning and end of each line down to 1·2, although the overall Snellen acuity was reduced to 0·33 by the 'crowding' phenomenon (Stuart and Burian, 1962). Crowding effects are absent in the Elidice test, which was passed by the amblyopic eye. If the data for this eye are neglected in the staff/patient comparison the differences are no longer significant at the 0·05 level (Table 2). This eye is also responsible for the non-zero percentage of eyes with a Snellen acuity of 0·33 passing on the Elidice (Table 1).

The present system enables an observer to pass the test by responding to only one orientation of the display, since a failure to answer is not recorded. This arrangement is suitable for a screening test for laser damage, since astigmatic observers can choose to respond only to those orientations which they can see clearly. Nevertheless, for some applications a forced choice test may be preferable, and this can be achieved by simple modifications to the answer gates and the result latch circuitry, so that the instrument counts correct answers and test presentations rather than wrong answers and responses, as in the present system.

The prototype displays the result of the test by illuminating either a red (for 'fail') or a green (for 'pass') LED indicator on the response panel. If a permanent record is required the result could be punched on a card, although this would increase the cost. The master reset function could then be achieved by arranging for the card to break a light beam (using a photon-coupled interrupter module) when it is inserted at the beginning of the test.

In the clinical trials described above the Elidice was used to determine whether a given clinically predetermined standard of visual acuity (in this case 1·0) was met. While a predetermined standard is universal in the case of driving test requirements, individual variations can be allowed for in the case of laser workers by so adjusting the visual angle of the Landolt-C on the apparatus as to make it appropriate to their clinically determined visual acuity. This can be done optically—for example, with two simple concave lenses—or geometrically by varying the viewing distance.

We thank Miss Janet Silver, Moorfields Eye Hospital, and her staff for help in supplying observers for the clinical trials, and the staff and patients for their co-operation.

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Band keratopathy with bilateral deafness as a presenting sign of hyperparathyroidism

M. PETROHELOS, D. TRICOULIS, AND P. DIAMANTACOS
From the Department of Ophthalmology, Evangelismos Medical Centre, Athens

SUMMARY An unusual case of hyperparathyroidism is reported in which calcification of the cornea was the presenting clinical and diagnostic sign. Early recognition of this condition may be of life-saving importance.

Calcification of the ocular tissues is fairly common and may occur either in cases of long-standing eye diseases or in systemic conditions causing alterations in the calcium and phosphate metabolism. In the majority of patients with hypercalcaemia the diagnosis has already been made, and the corneal and conjunctival deposits are found after careful examination by biomicroscopy. The purpose of this paper is to report a case of hyperparathyroidism in which the diagnosis was confirmed after the discovery of calcium deposits in the corneal and conjunctival tissues.

Case report

The patient was a housewife aged 24 who had been well up to about 18 months before admission to hospital. After a normal pregnancy and delivery she became nervous, irritable, and easily upset. About 8 months later she developed anorexia, nausea, vomiting, lost her appetite and lost weight, and suffered intermittent attacks of epigastric pain. A laparotomy was performed at that time and a diagnosis of acute pancreatitis was made. She was too weak to stand. Three months later she developed bilateral deafness, with marked decrease of vision and pronounced weakness and anorexia. She was placed on vitamin therapy, cortisone, and atropine eye drops. However, her condition steadily worsened until her admission to hospital. Her weight had dropped from a normal 130 to 69 lb (59 to 31 kg).

On the day of her admission to hospital physical examination showed a chronically ill woman who was deaf bilaterally and had lost much weight. She wore a hearing aid without effect.

On physical examination the blood pressure was 135/85 mmHg. The thyroid was of normal size and no masses or nodes could be felt in the neck. The heart was of normal size. An apical systolic murmur could be heard. The finger nails showed bands of whitish discoloration and softness at the nail bases. Reflexes were very active throughout. Examination of the eyes on the day of admission revealed bilateral band-shaped corneal opacities, symmetrical in both eyes, which extended along the palpebral fissures without a definitely clear zone separating them from the periphery. The vision was 6/30–1 OD and 6/9–2 OS. Examination with the slit lamp showed that the corneal opacities not only predominantly involved the palpebral fissures but extended to the lower portion of the cornea as well. A clear corneal zone of about 3 mm was present in the upper portion from 10 to 1 o'clock OU. The corneal changes consisted of a subepithelial diffuse collection of whitish material which was located in Bowman's membrane with direct focal illumination. The deep corneal layers were intact, and no vascularisation was present. The bulbar conjunctiva also showed glass-like subepithelial crystals temporally and nasally in the limbus. A diagnosis of band keratopathy, possibly due to hypercalcaemia, was made, and a biopsy of corneal and conjunctival tissues from the limbal area was done. The pathological report recorded a heavy deposit of crystalline material in the supporting tissue and beneath the epithelium. This substance took a pale blue stain with haemalum and eosin, indicating a probable calcium content.

Laboratory analysis showed the following serum values: serum calcium 16·2 mg (4·05 mmol/l), inorganic phosphorus 4·1 mg (1·3 mmol/l), alkaline phosphatase 10·5 units, non-protein nitrogen 44 mg (31·4 mmol/l), and total protein 6·0 g/100 ml (60 g/l) with an albumin-globulin ratio 2:3. The cerebro-

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spinal fluid calcium was 6·8 mg/100 ml (1·7 mmol/l).

Urine analysis showed a plus 1 reaction for albumin, 3 to 6 leucocytes, 0 to 3 red blood cells per m^3 and exretion of 624 to 785 mg (15·6 to 19·8 mmol) of calcium in 24 hours. Examination in the otology department revealed the tympanic membranes to be covered with thick whitish plaques bilaterally resulting in a severe perceptive deafness. Roentgenograms showed decalcification of the long bones and the lamina dura. The upper gastrointestinal tract was negative and no calculi were observed in the gall bladder or the kidneys.

With a possible diagnosis of parathyroid adenoma an exploratory examination of the neck was done. It disclosed the presence of a large parathyroid tumour measuring 1·5 × 1 cm in diameter, which was totally removed. Examination of the tumour showed it to be a parathyroid adenoma. The postoperative course was entirely uneventful. The patient's appetite increased remarkably, and with this she gained weight and a sense of well-being. A considerable improvement of the visual and auditory acuity was noticed. On the day of discharge the serum calcium was 10·7 mg/100 ml (2·7 mmol/l) with inorganic phosphorus 4·3 mg/100 ml (1·39 mmol/l) and alkaline phosphatase 11·5 units.

She was re-examined a month later, and at that time her vision was 6/6 OU and her hearing had returned to normal. Examination of the eyes with the slit lamp showed considerable reduction in the band keratopathy, with a practically clear pupillary area OU and only a residual opacity of about 2 mm in the limbal area temporally and nasally.

Discussion

The first reported observation on the deposition of calcium in the cornea and conjunctiva of patients with hyperparathyroidism is that of Walsh and Howard (1947).

Other workers supported this finding and reported a further series of patients (Cogan *et al.*, 1948; Walsh and Murray, 1953; Berkow *et al.*, 1968; Jensen, 1975). More recently Porter and Crombie (1973) described 4 patients in whom the diagnosis of hyperparathyroidism was confirmed after the discovery of calcium deposits in the cornea. Other systemic conditions producing calcification of the ocular tissues are well known, such as sarcoidosis, vitamin D intoxication, and chronic renal failure (Porter and Crombie, 1973). The ocular changes occur symmetrically in both eyes. In the conjunctiva the deposition of calcium variously described as white flecks or as glass-like crystals is primarily seen near the limbus running concentrically with the corneal margin. The corneal changes consist of a diffuse superficial milky opacity running as a band across the palpebral fissure.

The specific location of calcium in the cornea and conjunctiva differs in respect of the position in which it is deposited. Recent studies have shown that calcium salts are deposited intracellularly in patients with hyperparathyroidism, as opposed to the extracellular deposits in patients with renal failure and in band keratopathy without elevated blood calcium (Berkow *et al.*, 1968; Jensen, 1975). From several points of view the reported case is most interesting. The presenting symptoms were loss of vision and hearing, and the corneal changes provided the first clinical evidence of hyperparathyroidism. The deposition of calcium in the tympanic membranes is rare, and to our knowledge has not been previously associated with this condition.

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British Journal of Ophthalmology, 1977, **61**, 496–497

Colchicine suppression of corneal healing after strabismus surgery

BEN ZION BIEDNER, LEONARD ROTHKOFF, LUDWIG FRIEDMAN, AND CECELIA GELTMAN

From the Department of Ophthalmology, Soroka Medical Center, and Faculty of Health Sciences, Ben Gurion University of the Negev, Beersheva, Israel

SUMMARY Two patients who had previously undergone uneventful operations for strabismus showed healing of corneal dellen and erosion after withdrawal of colchicine therapy. It is suggested that the exhibition of colchicine therapy for familial Mediterranean fever in these two cases was responsible for initial persistence of these two postoperative complications.

The occurrence of corneal dellen is not uncommon after rectus muscle surgery, especially with the limbal approach (Tessler and Urist, 1975). The condition is usually transient and leaves no permanent effect. We recently operated on 2 children with strabismus who were receiving prophylactic colchicine therapy for familial Mediterranean fever. They both developed persistent marginal corneal lesions which healed only with cessation of colchicine.

Case reports

CASE 1

In January 1974 a 6-year-old boy underwent bilateral medial rectus recession and bilateral inferior oblique recession for a V esotropia using a limbal approach. The postoperative course was uneventful. Owing to recurrent attacks of familial Mediterranean fever a prophylactic course of colchicine therapy, 3 tablets daily, was begun in August 1975. Because of residual esotropia a bilateral lateral rectus resection using a limbal approach was performed in February 1976. On the first postoperative day shallow saucer-like excavations were seen at the temporal margins of both corneas. Bilaterally the lesions formed an ellipse, 2 mm × 1·5 mm, parallel to the limbus, with their borders clearly defined. The wall on the corneal side was steep, while the limbal wall was sloping. The bases of the lesions appeared hazy and dry with definite fluorescein staining. A diagnosis of postoperative dellen was made.

Patching and chloramphenicol ointment were tried for 2 days without effect. The boy continued as an outpatient, receiving only chloramphenicol ointment twice daily. At 4 weeks after operation no change was seen in the dellen. Treatment was changed to chloramphenicol drops 3 times daily. At 8 weeks after operation the dellen still persisted and were approximately one-third the stromal thickness in depth (Fig. 1). Because of our suspicion that colchicine might be implicated in the delayed healing treatment with this drug was stopped. Within 3 days the dellen had completely healed except for a slight subepithelial haze, which has persisted until the present.

CASE 2

A 13-year-old boy had previously undergone a bilateral medial rectus recession in December 1967, using a limbal approach. The postoperative course was uneventful. In October 1975 treatment had been started with colchicine, 3 tablets daily, for

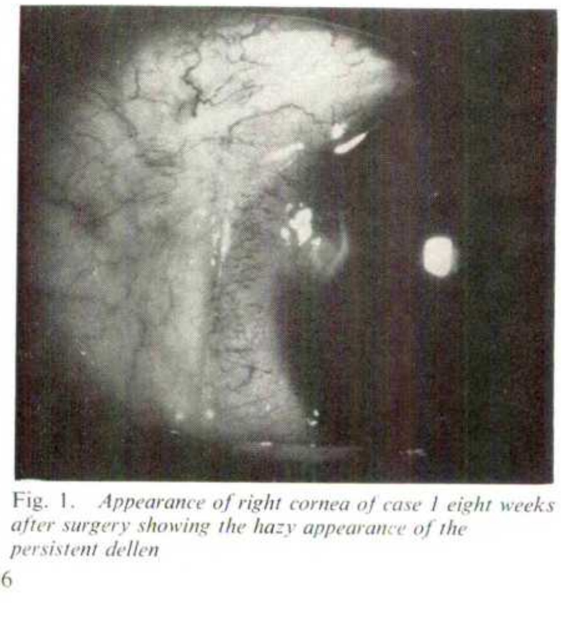

Fig. 1. *Appearance of right cornea of case 1 eight weeks after surgery showing the hazy appearance of the persistent dellen*

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prevention of attacks of familial Mediterranean fever. In December 1976 a bilateral lateral rectus resection was performed using a limbal approach for residual esotropia. On the first postoperative day a corneal erosion extending from 9 o'clock to 12 o'clock with fluorescein staining was present on the right cornea. The eye was treated with chloramphenicol ointment and patching, with no decrease in size or staining up to 3 weeks after operation. In consultation with the patient's paediatrician it was decided to discontinue the colchicine therapy. Healing of the corneal erosion was complete in 2 days without any residual defect.

Discussion

Colchicine is a well-documented antimitotic agent, arresting cell division in the metaphase. Cells with the highest rate of division are the most affected (Woodbury and Fingl, 1975). The effect of systemic colchicine in arresting corneal epithelium replication has previously been shown and has been used experimentally in studying corneal epithelial mitosis (Buschke *et al.*, 1943).

Familial Mediterranean fever is a disease of unknown origin characterised by recurrent attacks of fever and polyserositis (Wolff, 1974). Prophylactic treatment with colchicine has been shown to decrease the incidence of these attacks (Goldstein and Schwabe, 1974). Its specific mode of action in this regard is still unknown, though its interference with microtubule assembly, phagocytosis, and degranulation may be involved (Dinarello *et al.*, 1974). Some of the serious side effects noted have been azoospermia (Merlin, 1972), diarrhoea (Shanbrom and Rapoport, 1958), bone-marrow depression (Wallace, 1961), and chromosomal abnormalities (Ferreira and Buonicenti, 1968) apparently due to its effect on mitosis.

The limbal approach to muscle surgery has enjoyed popularity because of the reduction in scar tissue and easier access to the muscles (Von Noorden, 1968). However, swelling of limbal tissues may contribute to corneal dellen and other peripheral corneal inflammations (Aronson *et al.*, 1970). These are usually transient, but permanent scarring and vascularisation have been reported (Baum *et al.*, 1968). Dellen are particularly common after rectus muscle resections because of increased swelling of limbus tissues (Tessler and Urist, 1975).

In the 2 cases presented both had undergone uneventful extraocular muscle surgery before the institution of therapy with colchicine. Only after secondary surgery while receiving colchicine did peripheral dellen and a corneal erosion develop resistant to standard treatment. On cessation of colchicine healing was rapid. Since in dellen and erosions the integrity of the corneal epithelium and its ability to replicate are essential to the healing process (Duke-Elder and Leigh, 1965; Hogan and Zimmerman, 1962), it is not surprising that a potent antimitotic agent such as colchicine will delay repair.

It would seem prudent for patients undergoing operations for strabismus who are simultaneously receiving prophylactic colchicine therapy for familial Mediterranean fever either to abandon the limbal approach to the muscles or to discontinue the colchicine prior to surgery in consultation with the paediatrician or internist.

We wish to thank Mr David Grynspan for the photography, and Mrs Bilha Savell for technical assistance.

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Book reviews

Current Concepts in Ophthalmology. Vol. 5. Edited by H. E. KAUFMAN and T. J. ZIMMERMAN. 1976. Pp. 297, 157 figs., tables, refs. C. V. Mosby: St. Louis (£28·05)

This book consists of 18 chapters, varying in length from 5 to 35 pages, written by members of the staff of the Department of Ophthalmology of the University of Florida and by three invited contributors from other centres in the United States. It is intended to convey what the authors think is most important in terms of newer developments in ophthalmology, and the contents obviously reflect the interests of the department from which the book emanates, with a strong accent on corneal disease, contact lenses, optics, and glaucoma, though there are chapters on vitrectomy, exudative senile macular degeneration, and axoplasmic transport in the visual system.

Many of the chapters are practical in approach, particularly those on herpetic keratitis, antiviral agents, the management of corneal graft complications, corneal storage and handling, and two chapters on vitrectomy, one of which is entitled vitrectomy for the anterior segment surgeon. The views expressed are essentially personal ones, but nevertheless valuable. It is a little disappointing that only 5½ pages are devoted to senile macular degeneration, and in contrast to the chapters on anterior segment this chapter is largely derivative. The only other chapter dealing directly with the retina is entitled 'Retinal Stretch and Accommodation', and reports personal research by the author on induced obliquity of the retinal receptor cells during accommodation. This is an interesting observation, but in a book of this sort is perhaps dealt with at too great a length. Similarly, the 35 pages devoted to a detailed mathematical treatment of the optical effects of indentation procedures are an inappropriate choice for this book. Keratoconus is dealt with in great detail and also the use of bandage soft lenses and some of the defects which may arise in soft lenses during wear in a chapter headed 'Lensopathies'. The chapter on immune reactions in the eye is also a little disappointing, being limited to 6 pages; it is mainly a summary of basic immune reactions with a brief note on corneal allograft rejection.

In spite of these criticisms there is much of interest in the book, which reviews at some length and in some depth a number of growing points in ophthalmology. It will be of particular interest to those working on the anterior segment of the eye; apart from the chapter on retinal stretch and accommodation, those interested in the retina will find little new. The volume is fairly expensive, but will make a useful addition to the ophthalmologist's bookshelf.

W. S. FOULDS

Obituary

A. H. Levy, BA, MD, CM, FRCS, 1875–1977

Dr Aaron H. Levy, formerly consultant surgeon to Moorfields Eye Hospital, died on 31 March, at the age of 101. He was the subject of a congratulatory note when he attained his 100th birthday (*British Journal of Ophthalmology*, 1975, **59**, 607). He is survived by his son and daughter.

Notes

Conference in Chicago

The Alex E. Krill memorial conference of the Department of Ophthalmology of the University of Chicago will be held on 21 and 22 October 1977 at the Drake Hotel, Chicago, Illinois. The Krill memorial lecture will be delivered by Paul Henkind. Other guest speakers include Nicholas Douvas, Richard Green, Douglas Anderson, Herbert Kaufman, and Gunter von Noorden. Additional lectures will be given by speakers from the University of Chicago. Further information from Frederick A. Mausolf, MD, Department of Ophthalmology, University of Chicago, 950 East 59th Street, Chicago, Illinois 60637, USA.

Eye-Bank Association of America

The Eye-Bank Association of America will hold a scientific programme on Saturday 1 October 1977 from 9.00 a.m. to 12.30 p.m. at the Sheraton-Dallas Hotel preceding the AAOO meeting. Papers relating to corneal transplantation and eye bank techniques are solicited. Further details from R. D. Richards, MD, Department of Ophthalmology, University of Maryland Hospital, Baltimore, Maryland 21201, USA.

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Preliminary Announcement

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Japan Intraocular Implant Society

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Theme: Avoidance of Complications in Implant Surgery

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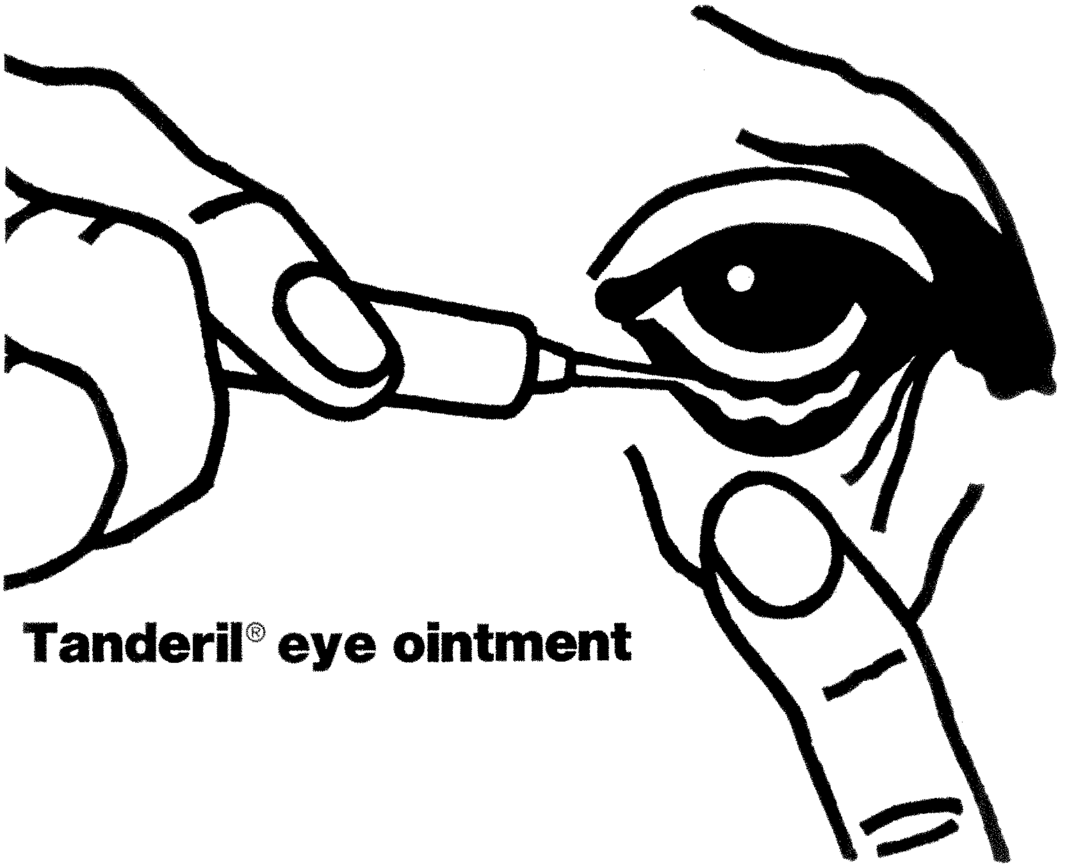

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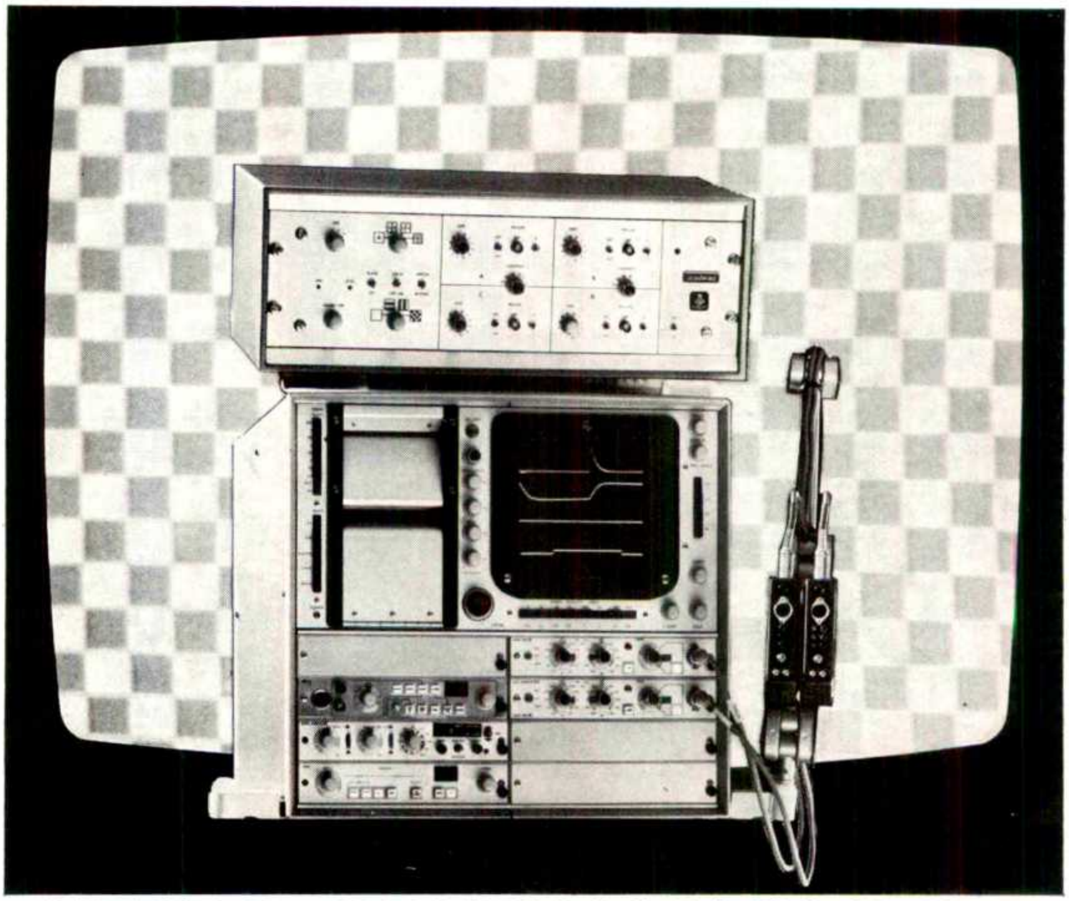

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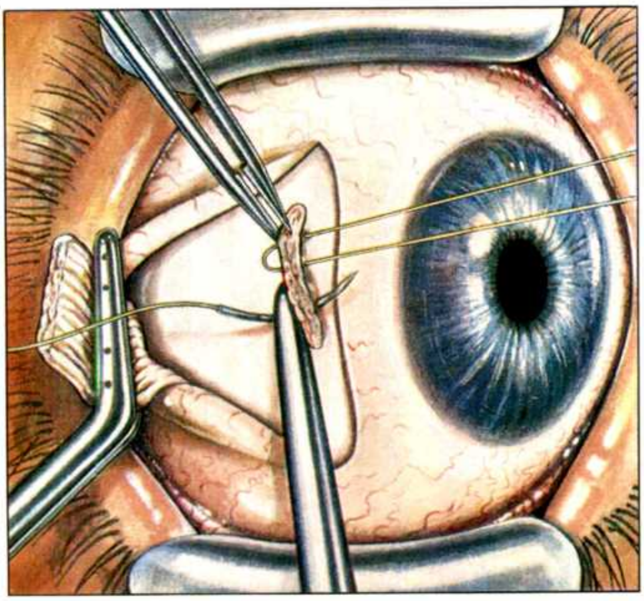

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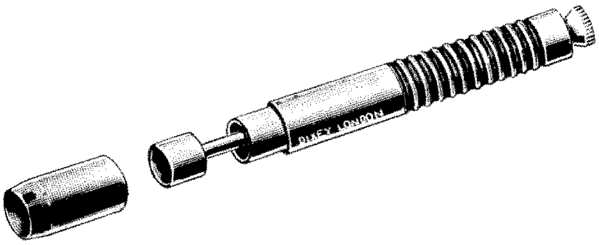

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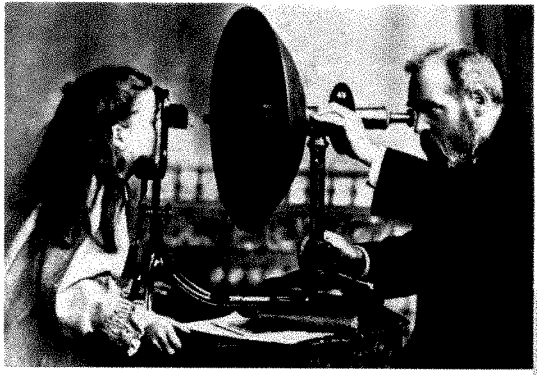

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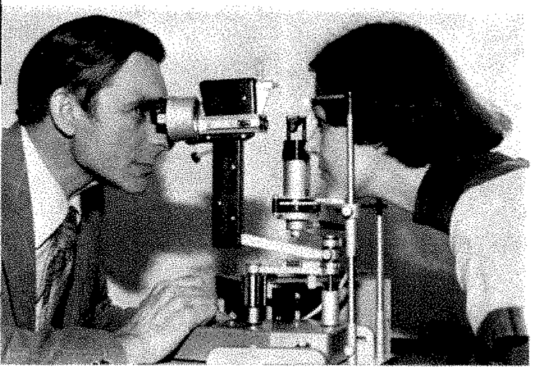

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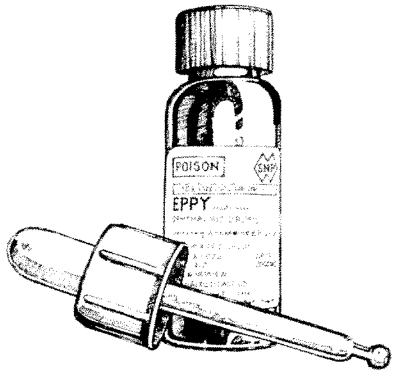

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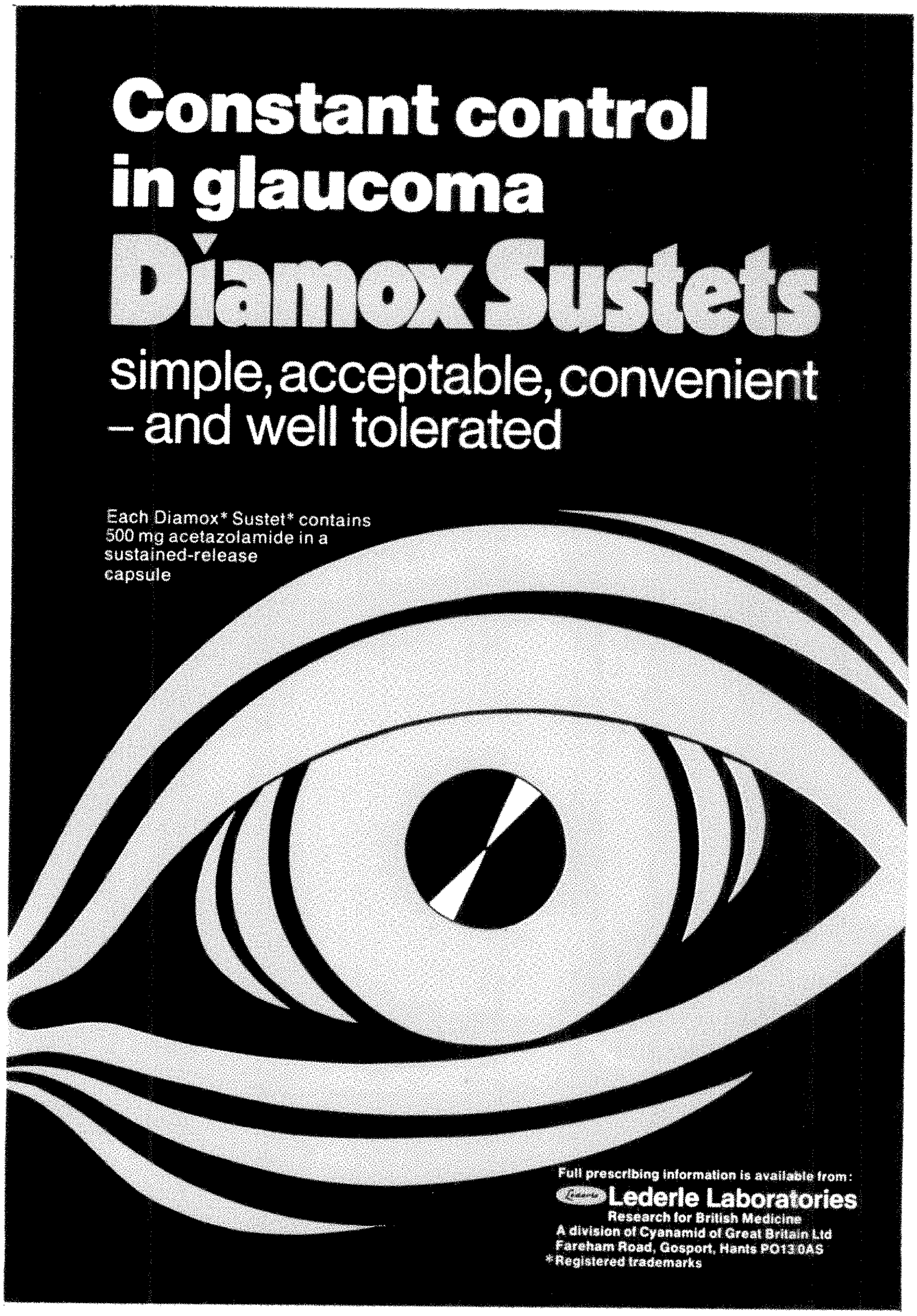

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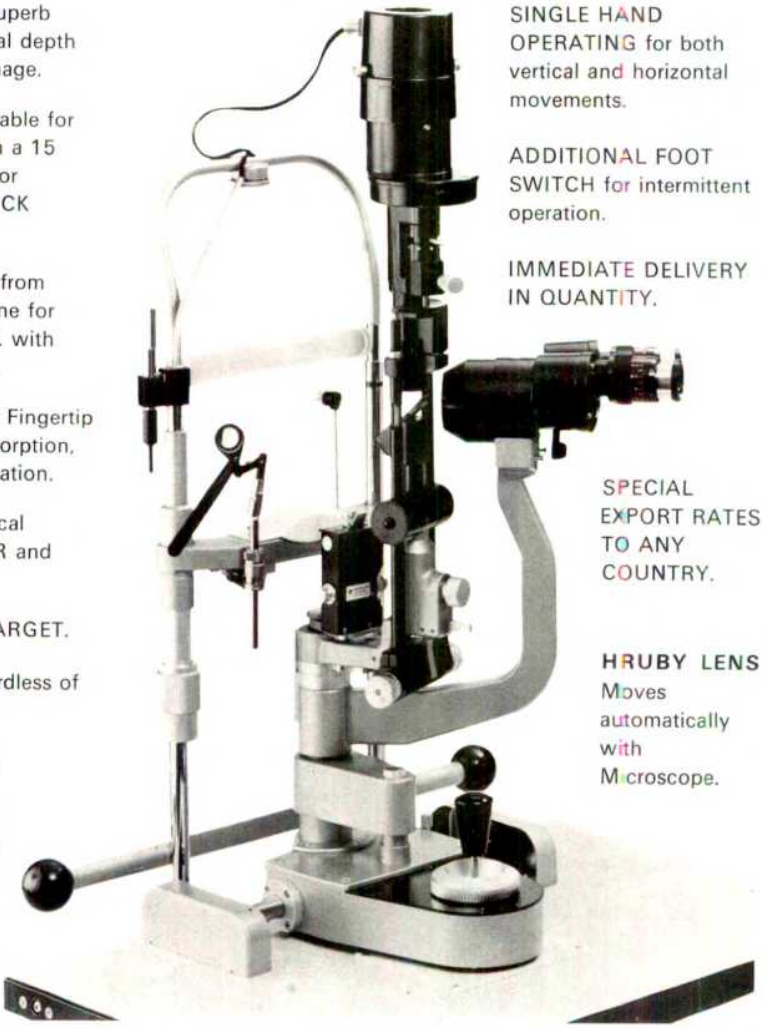

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British Journal of Ophthalmology, 1977, **61**, 553–554

Editorial: Photocoagulation for diabetic retinopathy

In medicine it is axiomatic that each advance in treatment brings a fresh crop of problems in its wake. The control of diabetes by insulin has done just this, and the increased prevalence of blindness due to diabetic retinopathy in the past two decades is one result. Accurate data are hard to come by, but the report of a committee set up by the British Diabetic Association (1969) estimated that in the United Kingdom there were about 5800 blind diabetics, of whom 44% were over 70 years of age, the prevalence being about 100 per million population or 1·9% of an estimated diabetic population of 300 000. Informal discussion suggests that the current population of diabetics under treatment may be nearer one million.

Faced with this threat of imminent blindness, often in the younger active patient, the introduction of photocoagulation by Meyer-Schwickerath (1959) seemed providential, for it enabled the safe destruction of much of the abnormal retinal vasculature with an apparent improvement of the fundus appearance. But photocoagulation is not without its risks, quite apart from the tragedies which may occur from inexperienced or careless application. Furthermore the natural history of diabetic retinopathy is variable, so the beneficial effect of photocoagulation can be assessed only by a controlled clinical trial, in which treated and untreated eyes, randomly allocated, are observed contemporaneously.

The interim results of two major multicentre trials in Britain and the United States have now been published (Multicentre Photocoagulation Trial, 1975, 1977; Diabetic Retinopathy Study Research Group, 1976). The British trial is concerned solely with xenon arc photocoagulation, while the United States trial also includes argon laser photocoagulation. A controlled trial devoted solely to the latter method of treatment is reported in the current issue of this journal by B. L. Hercules and colleagues (p. 555). The details of these reports should be studied in the original articles, but their message is clear. In proliferative diabetic retinopathy, with new vessels arising from the optic disc, treated eyes fare better than untreated in terms of vitreous haemorrhage and of maintained visual acuity over a follow-up of 2 or 3 years. These statistically significant results constitute a positive indication for treatment of those patients falling within the confines of the treated groups; outside these groups the indications are less clear. The treatment of peripheral new vessels shows some advantage, but here the time factor may be important, and a decisive result may not be seen until a 5-year follow-up is achieved. Late proliferative retinopathy with massive fibrosis and its complications appears to be uninfluenced.

In maculopathy, the subject of the first report from the Multicentre Photocoagulation Trial (1975), patients showed a decisive improvement in visual acuity after treatment provided the initial impairment was not too severe, but, disappointingly, there was a subsequent decline, which was, however, less than that of the control eyes. This result is in sharp contrast to the results in proliferative retinopathy, where the gap between the visual acuities of treated and control eyes widens with the passage of time owing to stabilisation of treated eyes and continued deterioration of control eyes.

All these trials have used the technique of panretinal photocoagulation for the treatment of proliferative diabetic retinopathy. This implies covering the whole fundus, with the exception of the macular area inside the temporal arcades, by a pattern of spaced photocoagulation burns which extend to the equator or beyond. This treatment usually results in a slight decline of visual acuity and some peripheral field loss in the treated eye, greater after xenon arc than argon laser photocoagulation. The relative effectiveness of the two modes of treatment has not yet been decided.

It is now imperative not only that each ophthalmologist should treat or arrange for the treatment of patients under his care with diabetic retinopathy, when their case is suitable, but that the national consequences of this obligation should be faced. This poses a formidable logistic problem: firstly, screening the diabetic population; and, secondly, assessing, treating, and following up those patients with proliferative retinopathy. A screening programme is essential if early proliferative changes are to be discovered, for they are usually symptomless. An annual review taking only 5 minutes of clinical time, if applied to the estimated million diabetics, would require the equivalent of 55 whole-time doctors to provide it. Possibly a way round can be found by the extensive use of technical assistance; even so the cost would be considerable. It is difficult to estimate how many new patients would require treatment each year. But if the figures for the registered blind are taken as a basis (for blindness is the ultimate fate of most untreated proliferative diabetic retinopathy), and allowance made for only 60% of blind diabetics being registered (British Diabetic Association, 1969) a conservative estimate of 1500 patients per annum emerges. If the entire management (assessment, treatment, and 5-year follow-up) could be achieved in 12 hours' clinical time, it would require the equivalent of 12 whole-time ophthalmologists, with adequate technical and nursing assistance, to provide this basic service, without any allowance for following up borderline cases, dealing with complications, or supervising screening procedures.

What priority such a programme can achieve in these times of financial stringency will emerge only in discussion with the Department of Health and Social Security, but it has the active attention of the British Diabetic Association, which is concerned by the present lack of facilities in many parts of the country.

At present three lines of activity should prepare for the time when treatment can be made available to every diabetic with retinopathy who needs it. First, pilot schemes and research into the best methods of screening are required; by analysing sample populations a better idea of the magnitude of the task and its therapeutic consequences would be gained. Secondly, ophthalmologists in training should be given more instruction in photocoagulation; and in-service teaching on the management of diabetic retinopathy should be available to both physicians and ophthalmologists. Thirdly, the many administrative problems associated with such a diabetic retinopathy service must be identified and solved.

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British Journal of Ophthalmology, 1977, **61**, 555–563

Peripheral retinal ablation in the treatment of proliferative diabetic retinopathy: a three-year interim report of a randomised, controlled study using the argon laser

B. L. HERCULES, I. I. GAYED, S. B. LUCAS, AND JULIE JEACOCK

From the University Department of Ophthalmology and Computational Group, Faculty of Medicine and Royal Eye Hospital, Manchester

SUMMARY A randomised controlled trial is reported of 94 patients with a symmetrical proliferative diabetic retinopathy involving the optic disc, who were treated by a peripheral retinal ablation technique using the argon laser. A highly significant difference in mean cumulative deterioration of visual acuity and blindness was shown in all but the late stages of the disease process between treated and untreated eyes. The untreated eyes exhibited far worse results. The earlier photocoagulation is initiated in the course of the proliferative process in this disease to control or preferably eliminate optic disc neovascularisation, the better the visual prognosis.

In England and Wales diabetic retinopathy is responsible for 7% of all new blind registrations and up to 20% in the middle-aged (Sorsby, 1972). Patients with the proliferative form of the disorder have been estimated by Deckert *et al.* (1967) and Caird *et al.* (1968) to progress to blindness in 50% of cases after five years. Taylor and Dobree (1970) noted that their patients with proliferative retinopathy had an incidence of optic disc neovascularisation of 68 to 73·25%.

Visual prognosis is far worse if the proliferative retinopathy involves the optic disc region (Deckert *et al.*, 1967); 50% of patients in this category are blind within two to three years. Neovascularisation of the optic disc frequently leads to vitreous haemorrhage and blindness (Patz and Berkow, 1968). In their three-year study Beetham *et al.* (1970) showed that 85% (29 patients) of untreated eyes with vitreous haemorrhage bled from new vessels at the optic disc. Caird *et al.* (1968) showed that after a vitreous haemorrhage one-third of involved eyes were blind within one year and one-third had vision which was permanently impaired. Patz and Berkow (1968) found that the second (good) eye in patients blind in the other eye frequently became blind through extension of the proliferative process in a short period of time (50% within one year). Meyer-Schwickerath (1954) showed that retinal changes in diabetes mellitus may be arrested or reversed by light coagulation. He further showed that regression could occur in newly formed vessels at retinal level even though treatment was remote from the lesion. Okun (1968); Krill *et al.* (1971a, b); and Taylor and Dobree (1970) noted regression of disc neovascularisation occasionally when extensive xenon-arc photocoagulation of the diabetic retina had been undertaken.

A circumferential ablation technique using the ruby laser was described first by Aiello *et al.* (1969). In a subsequent series (Beetham *et al.*, 1970) 30% of patients with optic disc neovascularisation showed significant reduction of new vessels after treatment. James and L'Esperance (1974) treated 52 eyes with proliferation at the optic disc by a retinal ablation technique with the argon laser. After treatment 42% of eyes showed obliteration of disc neovascularisation, and 33% showed a significant response.

Interim reports from a multicentre study in the United States using both xenon arc and argon laser (Diabetic Retinopathy Study Research Group, 1976) and England (British Multicentre Photocoagulation Trial, 1977) using only xenon arc photocoagulation indicate that photocoagulation confers real benefits on the treated eye. This difference between treated and untreated eyes was enhanced by previous vitreous haemorrhage, as, untreated, this has a poor

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prognosis. In a retrospective study Little *et al.* (1976) compared photocoagulation techniques in the treatment of proliferative diabetic retinopathy. 'Focal' treatment was found to be dangerous, 'feeder-frond' treatment was effective for only a short period, and 'pan-retinal' treatment was both safe and effective. In combination the last two techniques showed a marginal summation of effect.

In view of the suggestions of other workers, and before any of their results were available, a trial was initiated in Manchester in 1973 to attempt elimination of optic-disc neovascularisation in the diabetic patient by peripheral retinal ablation and to evaluate the effects of argon laser photocoagulation on the course of the disease.

Patients and methods

Those patients found on routine screening to have diabetic retinopathy were referred from general practitioners, diabetic clinics, and ophthalmic units in the north-west of England; 94 consecutive patients (56 men and 38 women) who conformed to the study protocol were admitted to the trial. The criteria for inclusion were (1) that both eyes of each patient were similarly affected by a proliferative diabetic process involving the optic disc; observable features of the retinopathy had to be within the same grade when each eye was classified (Table 1); (2) that visual acuity at initial assessment did not differ by more than two lines on the Snellen chart and was at least 6/24 in the worst eye.

Exclusion from the study was made if: (1) The patient's age was greater than 70 years; (2) life expectancy was possibly too short for subsequent assessments; (3) previous pituitary ablation had been undertaken; (4) either eye had received previous xenon arc photocoagulation; (5) intercurrent ocular disease was present; (6) visual acuity was adversely affected by opacities of the media and visual pathways, making retinal photography and treatment unsatisfactory; and (7) proliferation in the retina had reached the late cicatricial stage with localised traction detachment. Eight patients subsequently receiving treatment to the 'control' eye were removed from the study at that point.

Table 1 *Randomisation: population studies of patients in the trial*

Group	*1*	*1a*	*1q*	*2*	*3*	*Total*
Age (years): range	18–64	18–62	25–64	23–65	33–49	18–65
average	42·4	45	40·2	39·4	41·8	41
Diabetes: duration	2–40	4–36	2–40	5–31	10–32	2–40
mean and average duration	16·4	17·1	15·8	18·4	16·6	—
insulin-dependent	33	19	15	37	9	80
oral hypoglycaemics	9	6	3	4	1	14

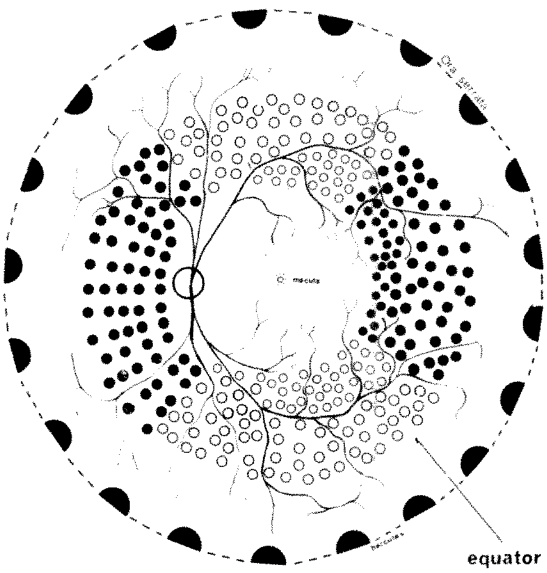

Fig. 1 *Technique of peripheral retinal ablation*

Key symbols:

○ 1st and 2nd } retinal quadrant treated, 500 μm spot burns
● 3rd and 4th }

● ○ Within macular arcades of vessels, 200 μm spot burns

TECHNIQUE

All treated eyes were subjected to extensive peripheral retinal photocoagulation by means of a Coherent 800 gas-argon laser, incorporating a 3-mirror Goldmann lens in the delivery system (L'Esperance, 1968) when necessary. The procedure was well tolerated after instillation of local anaesthetic drops in all except 2 patients, who required retrobulbar anaesthesia.

Photocoagulation burns were applied within the vascular arcades above and below the macula, but an approximately circular area of radius 2½ disc diameters, with the fovea at its centre and including the papulomacular bundle, was left untouched. In the nasal fundus photocoagulation was extended centrally to the edge of the optic disc and involved any new vessels arising from this margin. In all meridians photocoagulation was extended anteriorly to the equator using the 3-mirror lens (Fig. 1).

Individual burns with sufficient energy to accomplish minimal retinal blanching were applied so that the observer achieved a uniform response over the whole area being treated. Marker burns of 200 μm diameter were applied to delineate the central area which was to be avoided. Inside the vascular arcades the 200-μm spot diameter was used to create a burn pattern with one burn diameter between applications. Outside the arcades and nasally, the 500-μm spot diameter was used exclusively as far as the periphery. In the nasal sector burns were applied from the nasal edge of the optic disc to the equator in radial rows which followed the direction of the nerve fibres.

Energy levels between 0·2 and 0·6 watt were used, though most burns required 0·35 to 0·45 watt. Inferiorly higher energy levels were required than in any other area of the retina. Lower energies of 0·2 watt were almost invariably adequate within the macular vascular arcades of vessels, where the 200-μm spot was used. In other areas utilising the 500-μm spot levels up to 0·5 watt were usually required. To complete treatment over 2000 burns were applied to most patients (range 800 to 3000). The procedure usually required up to 6 sittings over a week (Fig. 2).

Retreatment of areas which appeared unduly lightly treated and of any patches of untreated retina within the 'target' area of the ablation procedure was undertaken in a number of patients in whom optic disc neovascularisation persisted, and in a small number in whom new vessels recurred. Finally, direct laser photocoagulation of middle- to large-sized retinal vessels was avoided, as 3 previous patients had had haemorrhages from such vessels at the time of treatment.

DATA RECORDED

Patients entering the trial received a full ophthalmic assessment including refraction, tonometry, visual fields, fundus photography, and fluorescein angiography. Patients were not excluded from the study group on the basis of nephropathy or other serious extraocular diabetic problems. However, during and after treatment every attempt was made to achieve good diabetic control by careful medical assessment. The eye to be treated was chosen at random and the untreated eye recorded as a control.

Evaluation of treatment was based on four main criteria: (1) Visual acuity: best corrected visual acuities were obtained at each visit, on subjective testing, by a refractionist who was not aware of the previous visual acuity nor the treated eye. (2) Appearance of the optic discs 6 months after treatment and yearly from that point. Assessment was aided by colour photographs and fluorescein angiograms. (3) Vitreous haemorrhage and other complications including uveitis, glaucoma, and retinal detachment. (4) Blindness: eyes were accepted as blind as an end result of the proliferative process and/or vitreous haemorrhage if this involved a fall of visual acuity to less than 6/60 on the Snellen chart. This result had to be recorded on at least two consecutive visits.

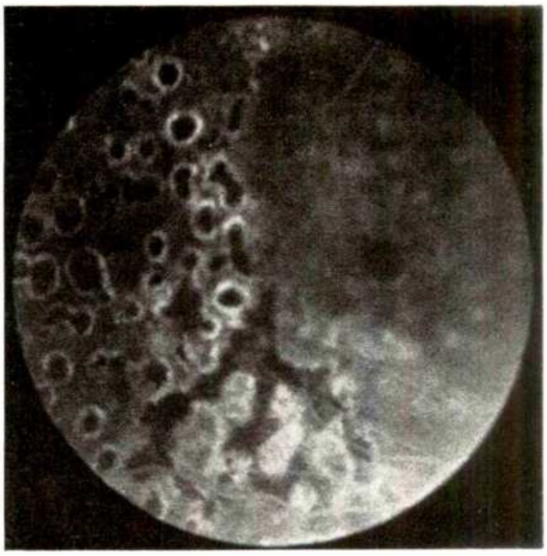

Fig. 2 *Fluorescein angiogram: laser scar pattern after peripheral retinal ablation*

Patients were reviewed at intervals of 2 weeks, 1 month, and 4 to 6 months after the completion of peripheral retinal ablation. Further assessment included visual fields, retinal colour photography, and fluorescein angiography.

CLASSIFICATION FOR DISC NEOVASCULARISATION

Patients were divided for the purpose of analysis of results into 3 groups. Selection depended on the ophthalmoscopic and photographic appearances of the neovascularisation at the optic disc at initial assessment. Comparisons were made at follow-up visits, but each patient retained his initial group position throughout the trial.

Group 1.—Disc neovascularisation with no gliosis (supporting connective tissue condensation). This corresponds to the anatomical description of early epi- and peripapillary neovascularisation (Fig. 3) (L'Esperance, 1973). This stage often shows little or no change for years, and occasionally spontaneous regression occurs (Larsen, 1960). This observation enabled a subdivision of the group, dependent on the behaviour of the control eye, after treatment.

Group 1 (a).—'Active', when the proliferative process at the optic disc in the control eye shows evidence of progression.

Group 1 (q).—'Quiescent', when there was either no change in the neovascularisation at the optic disc or spontaneous regression in the control eye.

Group 2.—Disc neovascularisation with gliosis and/or intravitreal proliferation (Figs. 4 and 5). This conforms to the later stages of epi- and peripapillary neovascularisation described by L'Esperance. Epipapillary changes can convert after marked glial proliferation to more widespread papillovitreal neovascularisation. The peripapillary type can extend 3 to 4 disc diameters across the retinal surface, and, again, can convert to the papillovitreal type. Fig. 5 shows the late phase of group 2 where the arcuate type of papillovitreal neovascularisation is developing.

Group 3.—Untreated grade 2 gradually passes into this stage of massive combined disc neovascu-

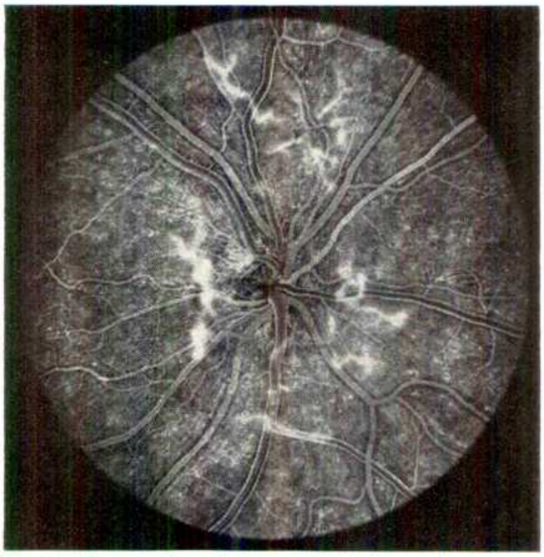

Fig. 3 *Fluorescein angiogram: Grade I optic disc neovascularisation*

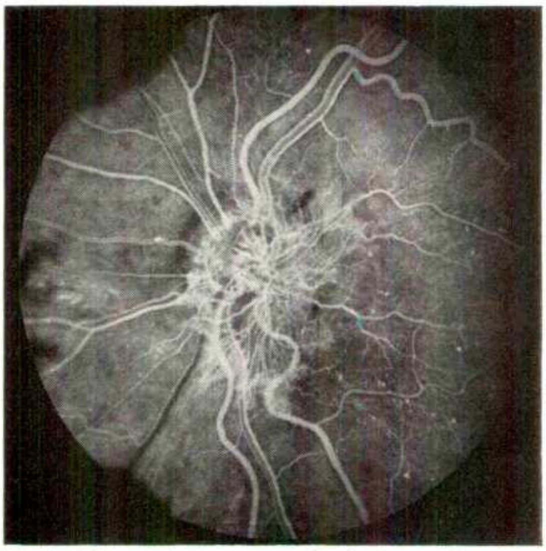

Fig. 4 *Fluorescein angiogram: Grade II optic disc neovascularisation. Early stage with onset of connective-tissue condensation in peri- and epipapillary new vessels*

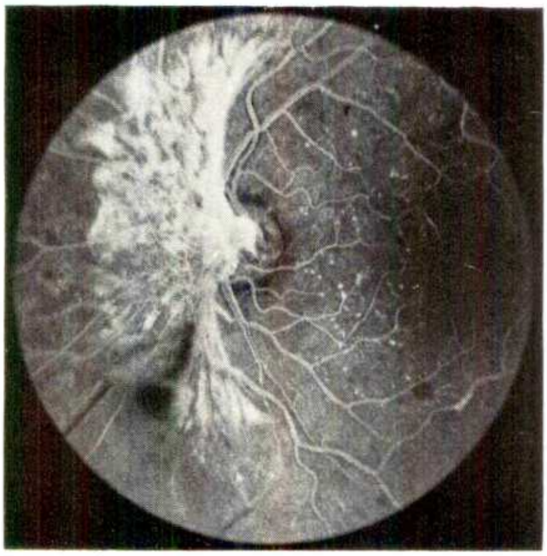

Fig. 5 *Fluorescein angiogram: grade II with transtemporal falciform fold of glial tissue (arcuate type of papillo-vitreal neovascularisation)*

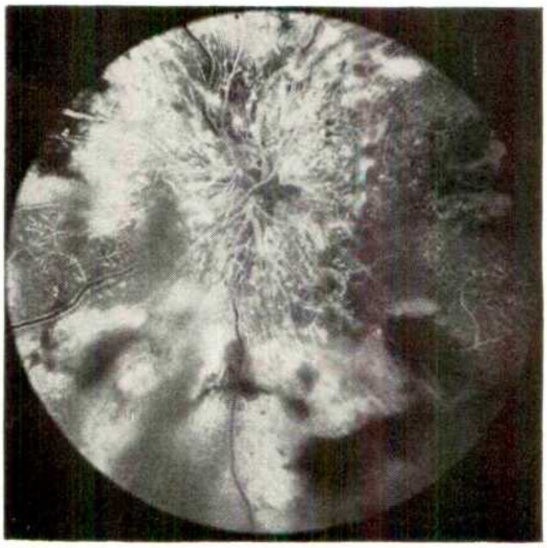

Fig. 6 *Fluorescein angiogram: grade III optic; disc neovascularisation with localised traction detachment*

larisation and condensed sheets or bands of connective tissue with significant vitreoretinal traction and/or localised retinal detachment (Fig. 6).

Results

No adverse effect of extrinsic factors (nephropathy, hypertension, etc.) on the results of photocoagulation influenced the study, because after randomisation of the eye to be treated we examined 'paired' eyes (see Table 2).

OPTIC DISC NEOVASCULARISATION

Regression of new vessels at the optic disc was achieved in a large number of patients. Each group responded differently to treatment ($\chi^2=52$, D.F. $=4$,

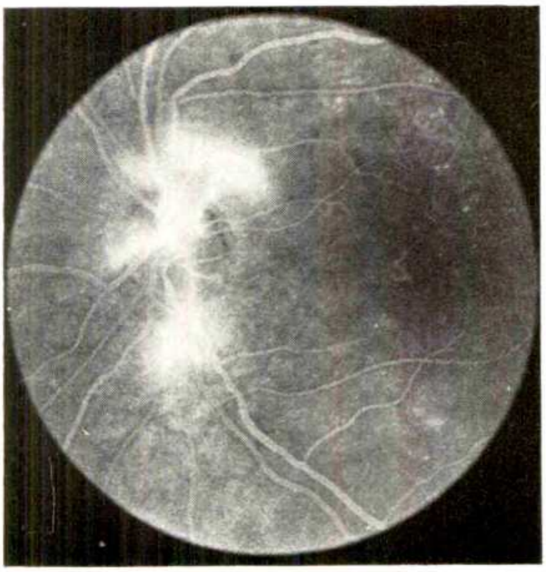

Fig. 7 *Fluorescein angiogram: grade I disc neovascularisation before treatment*

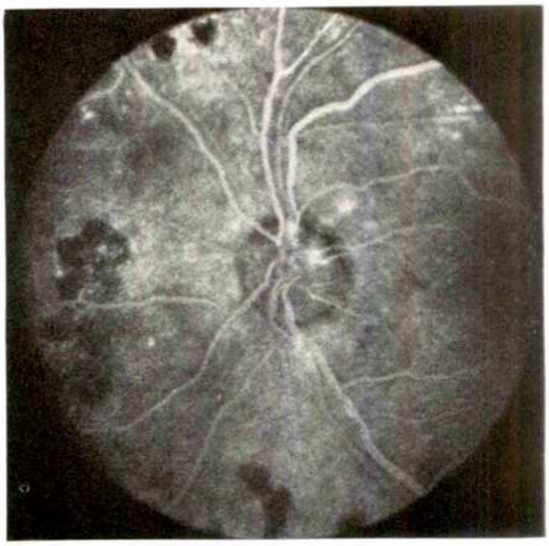

Fig. 8 *Fluorescein angiogram: previous optic disc 1 year after treatment, showing almost 100% regression of new vessels*

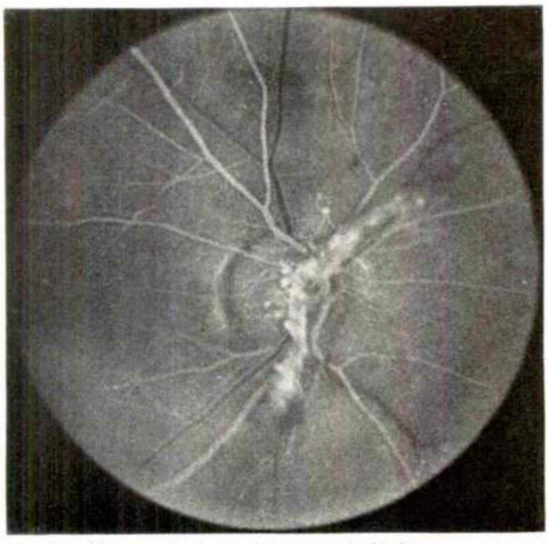

Fig. 9 *Fluorescein angiogram: grade II disc neovascularisation before treatment*

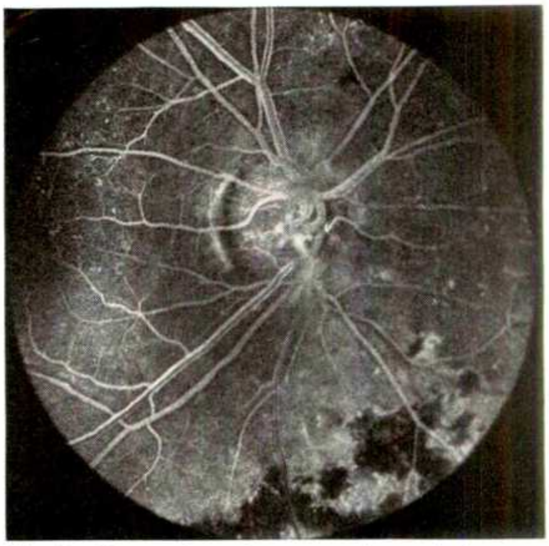

Fig. 10 *Fluorescein angiogram: previous optic disc 6 months after treatment, showing small glial scar and regression of new vessels*

$P < 0.001$). Table 2 shows that in 36% of all treated eyes new vessels disappeared completely or almost completely. Improvement was greatest in group 1 patients, where they disappeared in 26/43 (60%) of eyes. A significant improvement ($95 > R > 50$) occurred in a further 40% of eyes—all in groups 1 and 2. Only 2 out of 43 eyes in group 1 (4·7%) showed no significant response, while all 10 in group 3 showed this lack of marked improvement (see Figs 7, 8, 9, 10, 11, 12, 13, 14).

VISUAL ACUITY

In group 1 no difference could be shown by the Wilcoxon test in the mean cumulative deterioration in visual acuity between treated and control eyes. In group 2 the difference ranged from very highly

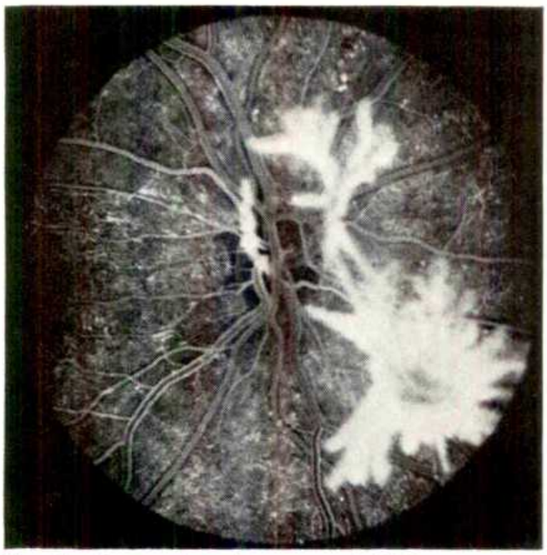

Fig. 11 *Fluorescein angiogram: grade II disc neovascularisation before treatment*

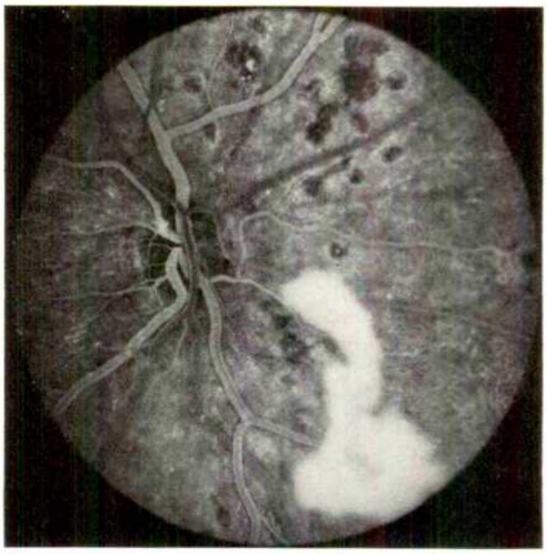

Fig. 12 *Fluorescein angiogram: previous optic disc 6 months after treatment, showing 75% regression of new vessels*

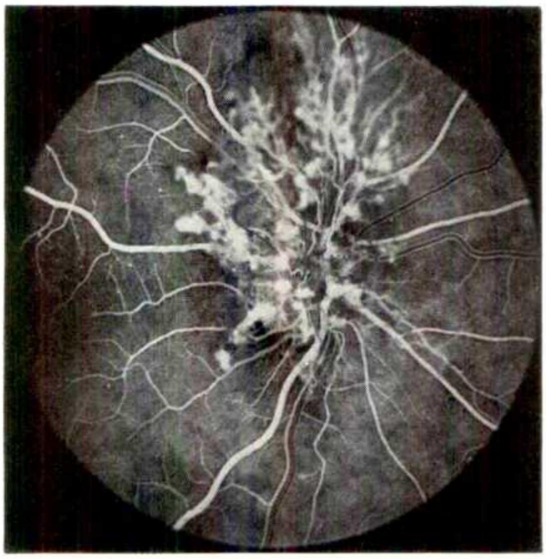

Fig. 13 *Fluorescein angiogram: grade II disc neovascularisation before treatment*

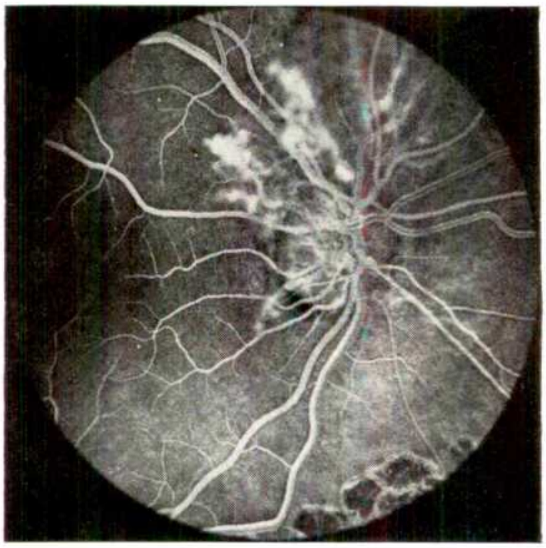

Fig. 14 *Fluorescein angiogram: previous disc 7 months after treatment, showing 50% regression of new vessels*

significant in the first year to significant in the second and third years. In group 3 there was no significant difference in mean cumulative deterioration between the treated and control eyes (Fig. 15 and Table 3).

Group 1 was divided on clinical grounds into 'active' (1*a*) and 'quiescent' (1*q*) subgroups. Wilcoxon tests were then applied to the treated and control eyes in both subgroups for each year. In both cases no significant difference could be demonstrated (P > 0·10). Examination of the resultant graphs suggested that there was no marked divergence between the treated and control means of the quiescent group with time and that this inability to demonstrate significance by the Wilcoxon test in the active group was due to the small sample sizes. Therefore the quiescent group (1*q*) was pooled, and a Mann-Whitney U-test applied. This showed a significant difference between the active (1*a*) untreated subgroup and the pooled quiescent group. There was, however, no significant difference between the active (1*a*) treated group and the pooled quiescent group (Fig. 16 and Table 4).

Table 2 *Comparison of the response of optic neovascularisation to treatment*

	Regression of optic disc new vessels			
Group	*R > 95*	*95 > R > 50*	*R < 50*	*n*
1	26	15	2	43
2	7	22	10	39
3	0	0	10	10
Total				92

R = % regression

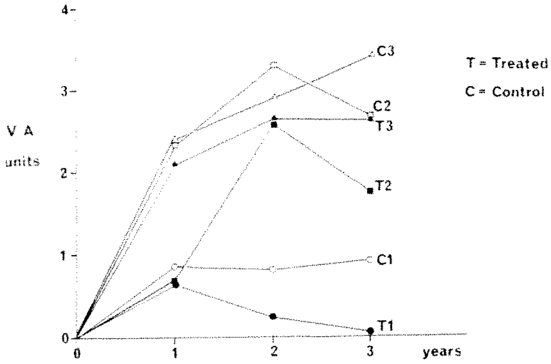

Fig. 15 *Mean cumulative deterioration in visual acuity for control and treated eyes in all groups*

Table 3 *Mean cumulative deterioration of visual acuity (VA units)*

	Year	*Treated*	*Control*	*n*	*P**
	1	0·62	0·85	39	>0·1
Group 1	2	0·24	0·83	29	>0·1
	3	0·08	0·92	13	>0·1
	1	0·63	2·34	41	<0·0009
Group 2	2	2·56	3·30	25	<0·005
	3	1·76	2·60	10	<0·025
	1	2·10	2·40	10	>0·1
Group 3	2	2·60	2·90	6	>0·1
	3	2·60	3·40	4	†

*Wilcoxon signed ranks matched pair test (one-tail probabilities)
†Insufficient data

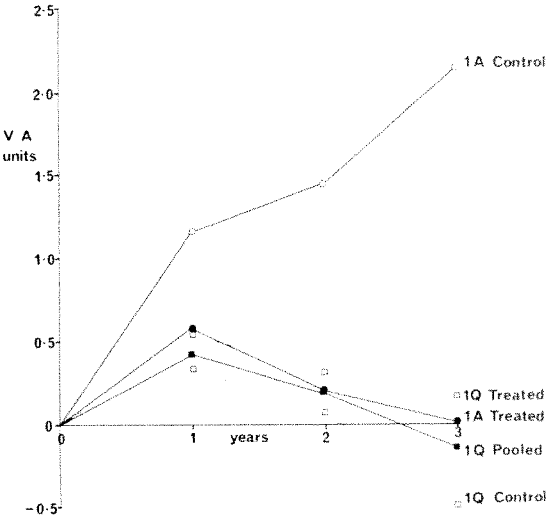

Fig. 16 *Mean cumulative deterioration in visual acuity for group 1 active and quiescent subgroups*

Table 4 *Mean cumulative deterioration of visual acuity for group 1 active and quiescent subgroups*

Active treated/quiescent pooled

Year	*Active T*	*n*	*Quiescent P*	*n*	*P**
1	0·58	24	0·43	30	>0·48
2	0·19	16	0·19	26	>0·31
3	0·0	7	−0·17	12	>0·10

Active control/quiescent pooled

Year	*Active C*	*n*	*Quiescent P*	*n*	*P**
1	1·17	24	0·43	30	>0·3
2	1·44	16	0·19	26	<0·06
3	2·14	7	−0·17	12	<0·025

*Mann-Whitney U-test (one-tail probabilities)

VITREOUS HAEMORRHAGE

The mean time to the onset of vitreous haemorrhage from the start of treatment was evaluated in treated and control eyes. The difference in mean time to vitreous haemorrhage, expressed in years, for all treated groups and for the control groups was very highly significant (Mann-Whitney U-test, P < 0·0001) (Table 5). When the mean time to vitreous haemorrhage between each of the treated groups was compared (Table 6), there was no significant difference between them (Kruskal-Wallis one-way analysis of variance, P > 0·1). When the control groups were compared there was also no significant difference between the groups (Kruskal-Wallis, P > 0·95). It was shown that there were fewer vitreous haemorrhages (χ^2=3·52, D.F. = 1, P=0·06), and that there was a longer time to the onset of such events in treated eyes than in control eyes.

BLINDNESS

The difference in proportions between treated and control eyes proceeding to blindness within 3 years was significant in groups 1 and 2. No significant difference was demonstrated in group 3 (McNemar's modified χ^2-test) (Table 7).

COMPLICATIONS

Early complications immediately following treatment were unusual. Some patients had transient myopia which resolved in a few days, and occasional patients suffered an equally transient mild uveitis. Peripheral field loss was initially as much as 15 degrees, reducing to 8 or 10 degrees within a month of treatment. Two patients suffered thrombotic glaucoma and 1 patient a retinal detachment, which was repaired.

Table 5 *Comparison of mean times to vitreous haemorrhage from start of treatment in treated and control eyes*

Treated	*n*	*Control*	*n*	*P**
1·42	24	0·74	40	< 0·0001

*Mann-Whitney U-test (one-tail probabilities)

Table 6 *Comparison of mean times to vitreous haemorrhage between groups for control and treated eyes*

	Group 1	*n*	*Group 2*	*n*	*Group 3*	*n*	*P**
Treated	1·44	9	1·79	7	1·06	8	> 0·10
Control	0·70	15	0·79	19	0·67	6	> 0·95

*Kruskal-Wallis (one-tail probabilities)

Table 7 *Summary of patients proceeding to blindness within 3 years*

Outcome	*Group 1*	*Group 2*	*Group 3*
Both blind	1	2	3
Treated blind – control sighted	0	1	0
Control blind – treated sighted	7	20	3
Both sighted	35	18	4
Totals	43	41	10
McNemar's test χ^2	5·14	15·43	0·33
P	< 0·025	< 0·0005	> 0·25

Discussion

Our findings support the views expressed by Beetham *et al.* (1970); James and L'Esperance (1974); and the Diabetic Retinopathy Study Group (1976) that a retinal ablation technique is effective in reversing the process of neovascularisation at the optic disc, and that photocoagulation is of greatest value in eyes at the earlier stages of the proliferative retinopathy. The earlier a patient was treated in the course of the proliferative retinopathy, the more likelihood of clinically significant regression of optic disc neovascularisation. As new vessels at the optic disc have been shown to have such a poor prognosis, total or significant regression would appear to confer some beneficial effects on the treated eye.

The findings of Caird *et al.* (1968) on the visual prognosis after a single vitreous haemorrhage illustrate the seriousness of this complication for vision. We have found that blindness will follow a vitreous haemorrhage as (1) a consequence of advancing cicatricial proliferative retinopathy; (2) failure of resorption of an extensive vitreous haemorrhage; (3) multiple vitreous haemorrhages; and (4) rarely a secondary glaucoma. We have shown that fewer treated eyes had vitreous haemorrhages, and that these arose much later in treated than in untreated eyes. This indicates that visual acuity may be retained for a significantly longer period after such events in treated eyes. The American study also suggested that vitreous haemorrhages in treated eyes resolved more rapidly than in untreated eyes. Better vision was retained in treated eyes from early optic disc neovascularisation to the onset of the late cicatricial stage. However, some cases with early epi- or peripapillary neovascularisation at the optic disc appeared to be in a quiescent phase. Treated eyes in the earlier stages of the proliferative process acted in the same way as these quiescent eyes and appeared to have been transformed into this stage while there was no progression. Treated eyes in the full-blown late cicatricial stage appeared to behave in the same way as untreated eyes. It is possible that careful treatment of the new vessels directly may improve prognosis for vision in this late group. Treatment of quiescent group 1 and also group 3 eyes was not shown to have significant deleterious effects on the eye. In view of this we would advise early treatment of all diabetics who are found to have neovascularisation at the optic disc.

Treatment in all cases should be adequate, and careful monitoring is necessary when this is accomplished. There are a significant number of patients who either achieve a less than desirable regression of new vessels or suffer a recurrence of the condition. These patients should receive timely repeat treatment.

Our thanks are due to Dr E. S. Rosen at the Manchester Royal Eye Hospital, and Dr Eva Kohner at the Royal Postgraduate Medical School, Hammersmith, for their interest and advice regarding this study; to Miss M. McDermott and Mr J. Sutton for help in the treatment of patients, and Miss Jayne Hughes for her work in the preparation of the paper. Our thanks are also due to Mr E. Young and Mr S. Shaw for their excellent photography.

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Observations on the retinal pigment epithelium and retinal macrophages in experimental retinal detachment

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SUMMARY After experimental retinal detachment in rabbits macrophages are a prominent feature in the subretinal space or within the retina. Two sources for these macrophages are identified. The retinal pigment epithelium (RPE) may undergo metaplasia and actively 'bud'; the evolving macrophage is then formed by a vitreal protrusion of the cytoplasm of an RPE cell which is 'nipped off' by lateral protrusions from adjacent cells. In addition, in regions of RPE proliferation, blood-borne cells were found in Bruch's membrane and among the mass of proliferated RPE cells, suggesting that blood-borne cells may pass from the choroidal circulation through Bruch's membrane and the RPE layer.

A distressing and still relatively unexplained complication of retinal detachment is the occasional occurrence after apparently successful surgery of gross fibrotic changes in the retina and vitreous leading to the clinical picture of massive vitreous retraction, or massive periretinal proliferation as it has been more recently termed (Machemer and Laqua, 1975). It has been suggested that cells originating from pigment epithelium may play an important role in the formation of periretinal membranes. It has been shown that intravitreal autotransplants of retinal pigment epithelium (RPE) may transform to cells having many of the characteristics of macrophages seen in experimental retinal detachment (Mandelcorn *et al.*, 1975). But the mechanisms underlying the formation of these macrophages are speculative.

During an investigation into the distribution of acid mucopolysaccharides in detached retinae (Johnson and Foulds, 1976) it became apparent that the retinal pigment epithelium may be actively involved in the formation of macrophages. This paper describes the possible roles of the RPE in the formation of such cells.

Material and Methods

For this investigation 7 adult Dutch rabbits weighing between 1·6 and 2·2 kg were used. Detachment of the retina was produced by a modification of the technique reported by Foulds (1963). The animals were anaesthetised with intraperitoneal pentobarbital (Nembutal), 60 mg/kg. The pupil of one eye of each animal was maximally dilated with several drops of 1·0% cyclopentolate and 10% phenylephrine. The collagen framework of the posterior cortical vitreous was destroyed by the rotation of a blunted 23 gauge needle introduced into the vitreous cavity via the pars plana under direct vision through a contact lens with an operating microscope. In contrast to the original technique no hyaluronidase was injected. A hole in the retina was created by suction through the needle, and this resulted in a subtotal detachment of the retina. The other eye remained normal and acted as the control. Two animals were killed after 1 week, 1 after 2 weeks, and 4 animals after 3 weeks. The animals were killed by an overdose of pentobarbital. The eyes were enucleated and bisected in the equatorial plane; the posterior halves were immersed in fixative at room temperature. The fixative was 3% glutaraldehyde buffered in Sorensen's phosphate buffer (pH 7·3). Tissue was taken from the attached and detached areas of the test eyes and corresponding positions in the control eye and conventionally processed for electron microscopy. The tissue was embedded in Spurr's resin. Sections 1 μm thick were stained with Loeffler's methylene blue for light microscopy. Sections 50–70 nm thick were stained with uranyl acetate and lead citrate and examined with a Philips 301 electron microscope.

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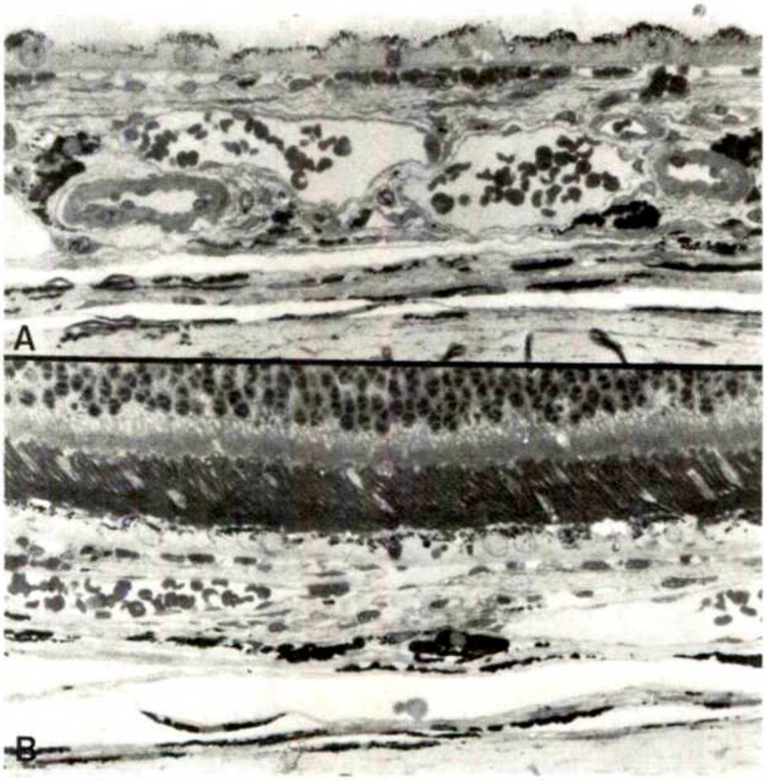


Fig. 1 *Appearance of pigment epithelium under detached retina* (A) *and attached retina* (B). *In the areas shown the pigment epithelium under the detached retina retains a normal appearance* ×640

Results

There were no discernible differences in the appearance of the pigment epithelium from tissues taken at 1 week, 2 weeks, or 3 weeks after the production of a retinal detachment.

Examination of the pigment epithelium in areas where the retina was detached showed considerable variation in the appearance of the RPE in the same eye. In some regions the RPE under the detached retina retained a near normal appearance, which by light microscopy did not differ from RPE under normal attached retina (Fig. 1). By electron microscopy only slight ultrastructural changes were seen in these near-normal areas of pigment epithelium (Fig. 2). The apical processes were disorganised and more numerous than in the control tissue. Unlike normal RPE, where the mitochondria are found predominantly adjacent to the basal infoldings, the mitochondria were randomly distributed throughout the cytoplasm. The cytoplasm was generally devoid of phagosomes containing recognisable outer segment material. The cells completely covered Bruch's membrane, and the lateral junctional complexes appeared to be intact. These findings are similar to those described in the owl monkey (Kroll and Machemer, 1968), in the rabbit (Ohkuma, 1973), in the rat (Reich-d'Almeida and Hockley, 1975) and after secondary detachments in man (Kroll, 1969).

In other areas, although the pigment epithelium remained as a single layer, the individual cells showed gross abnormality with a vitreal displacement of the cytoplasm (Fig. 3). In addition, free pigmented cells were seen adjacent to the apical surface of the RPE layer. This considerable disturbance in the RPE was well seen on electron microscopy. In the areas being considered Bruch's membrane remained covered by RPE, but the individual RPE cells were affected by a cytoplasmic displacement which took a variety of forms; these could be placed into a sequence which may represent the formation of free macrophages from the RPE (Figs. 4–7).

The initial change from the flat uniform RPE cell was an alteration in cell shape. The apical surface of an RPE cell became convex (Fig. 4). This convexity became more marked (Fig. 5), and two ad-

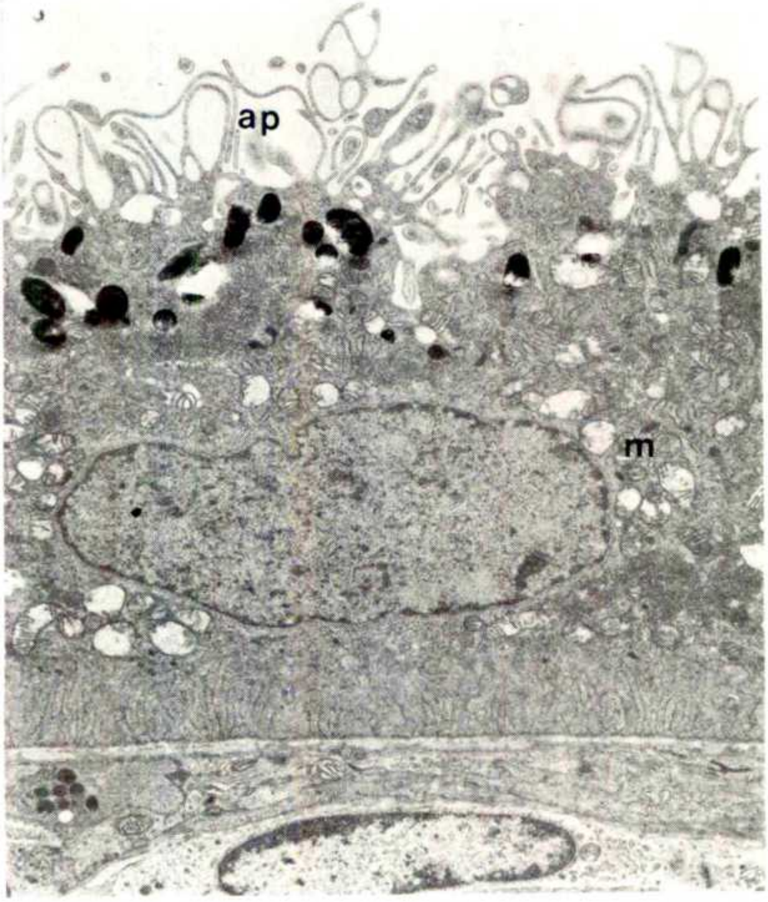


Fig. 2 *Electron micrograph from same area as shown in Fig. 1A. The mitochondria* (M) *are randomly distributed throughout the cytoplasm. The apical processes* (AP) *are more numerous than normal* ×5570

jacent RPE cells pushed out lateral cytoplasmic protrusions which pinched in the basal part of the vitreally displaced cytoplasm (Fig. 6). Eventually the lateral processes of the adjacent cells 'nipped off' the remaining cytoplasm and resulted in the formation of a free cell, leaving the remaining portion of the cell cytoplasm still attached to Bruch's membrane (Fig. 7). The vitreally displaced cytoplasm and the free cell generally possessed a nucleus in every cell section studied. In these regions the lateral cell junctions were often more complicated than normal with the occurrence of a larger number of adhering type junctions. The free cells often contained melanin granules and had many characteristics of the underlying RPE. On occasion, however, some of the free cells had a lower cytoplasmic electron density than the RPE, and the pigment granules were confined to what appeared to be a secondary lysosomal complex

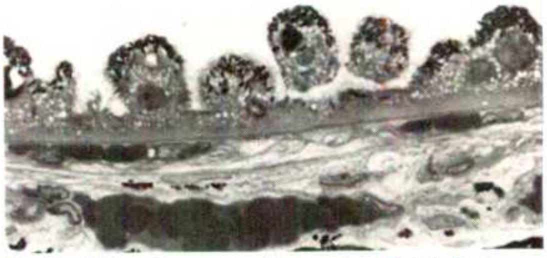
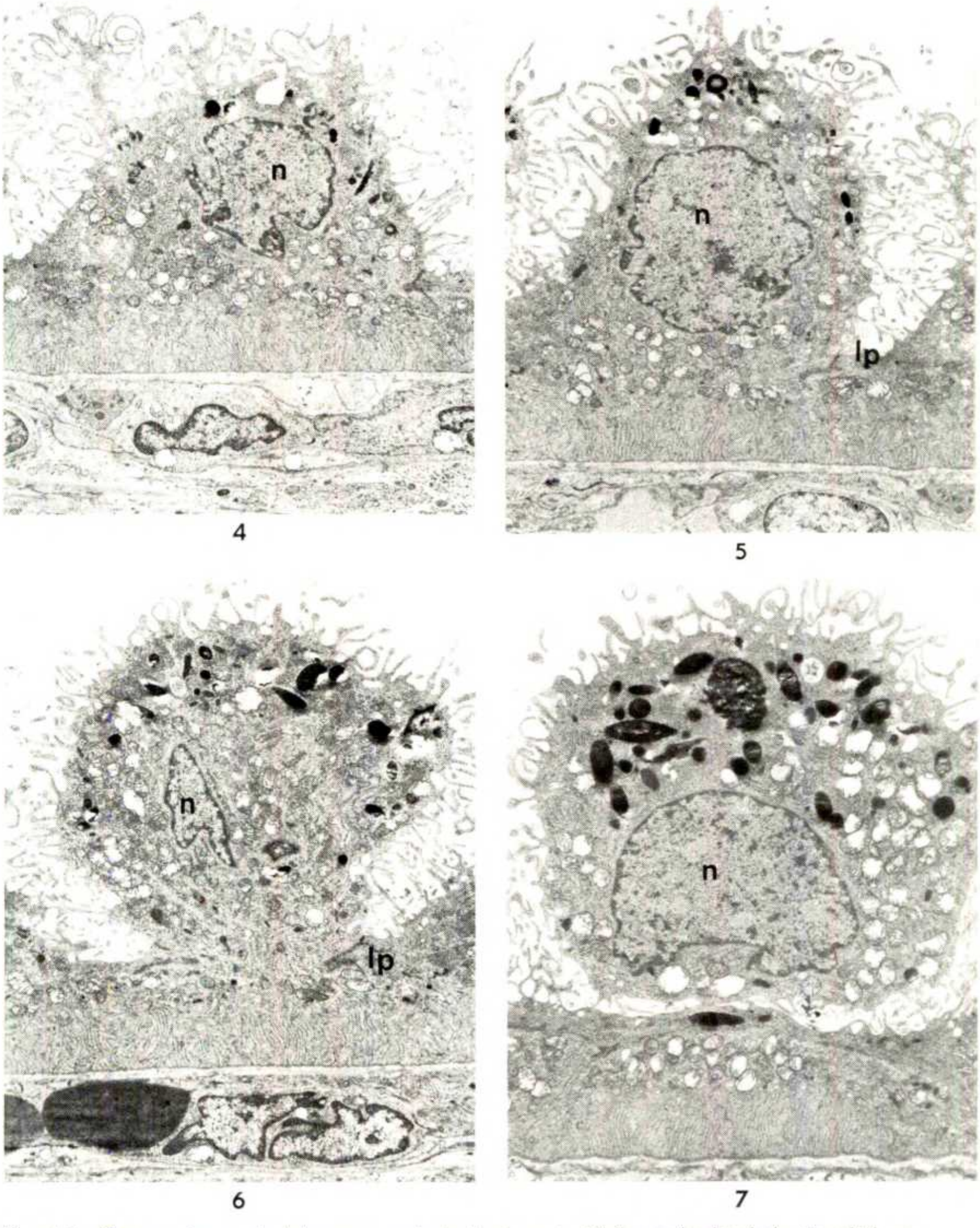


Fig. 3 *Light micrograph of pigment epithelial layer under detached retina to show irregularity of epithelial cells with cytoplasmic displacement towards the vitreous* ×1300



Figs. 4–7 *Electron micrograph of changes occurring in the pigment epithelium under detached retina which may represent a sequence of events leading to the formation of free macrophages.* N = *pigment epithelial cell nucleus.* LP = *Lateral processes of neighbouring pigment epithelial cells* × 5260

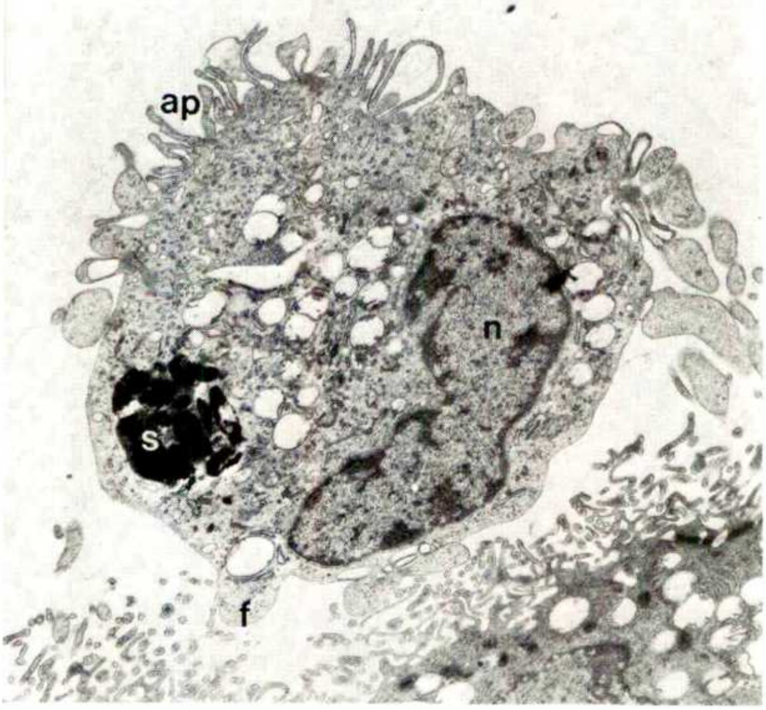


Fig. 8 *Electron micrograph of free cell adjacent to RPE. The cell possesses finger-like processes similar to the underlying RPE in addition to filopodia typical of macrophages. Pigment granules are contained in a secondary lysosomal complex.* F = *Filopodia.* AP = *Apical processes.* N = *nucleus.* S = *Secondary lysosomal complex containing pigment* ×9600

(Fig. 8). In the majority of free cells the prominent processes normally seen on the surface of an RPE cell were reduced in number and absent over large areas; however, filopodia were often present. Ultrastructurally such cells appeared half way between a pigment epithelial cell and a free macrophage. This process is shown in schematic form in Fig. 9.

In yet other areas under the detached retina the RPE proliferated to form a layer several cells thick. By light microscopy these cells were seen to be pigmented and spindle-shaped with their long axes parallel to Bruch's membrane (Fig. 10). By electron microscopy it could be seen that the proliferated cells constituted a tight framework, with many cell

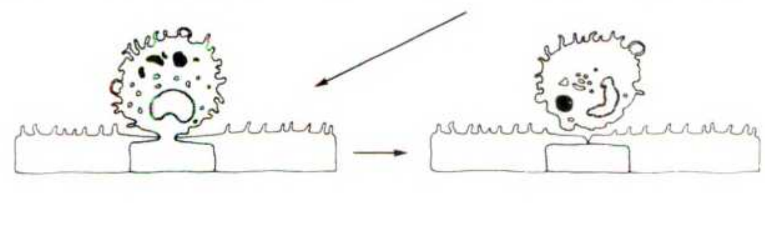


Fig. 9 *Diagram of suggested sequence of events leading to the formation of free macrophages from pigment epithelial cells*

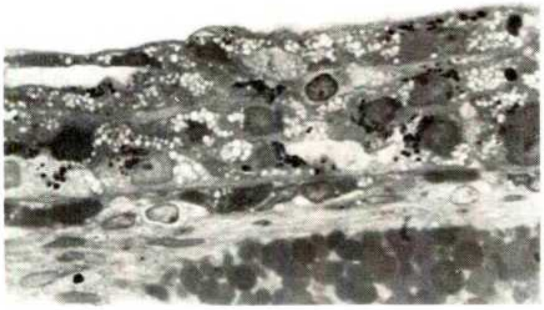


Fig. 10 *Light micrograph of RPE underlying detached retina to show an area where RPE cells have proliferated to form a layer several cells thick* ×650

junctions between adjacent cells (Fig. 11). The cells adjacent to Bruch's membrane were often irregular in shape, and many appeared to be involved in a similar series of events leading to the formation of free cells as already described. Bruch's membrane was completely covered by RPE, though in places the covering was attenuated. Bruch's membrane underlying the proliferated RPE was considerably thicker than normal (Fig. 12). Among the framework of pigmented cells and in the thickened Bruch's

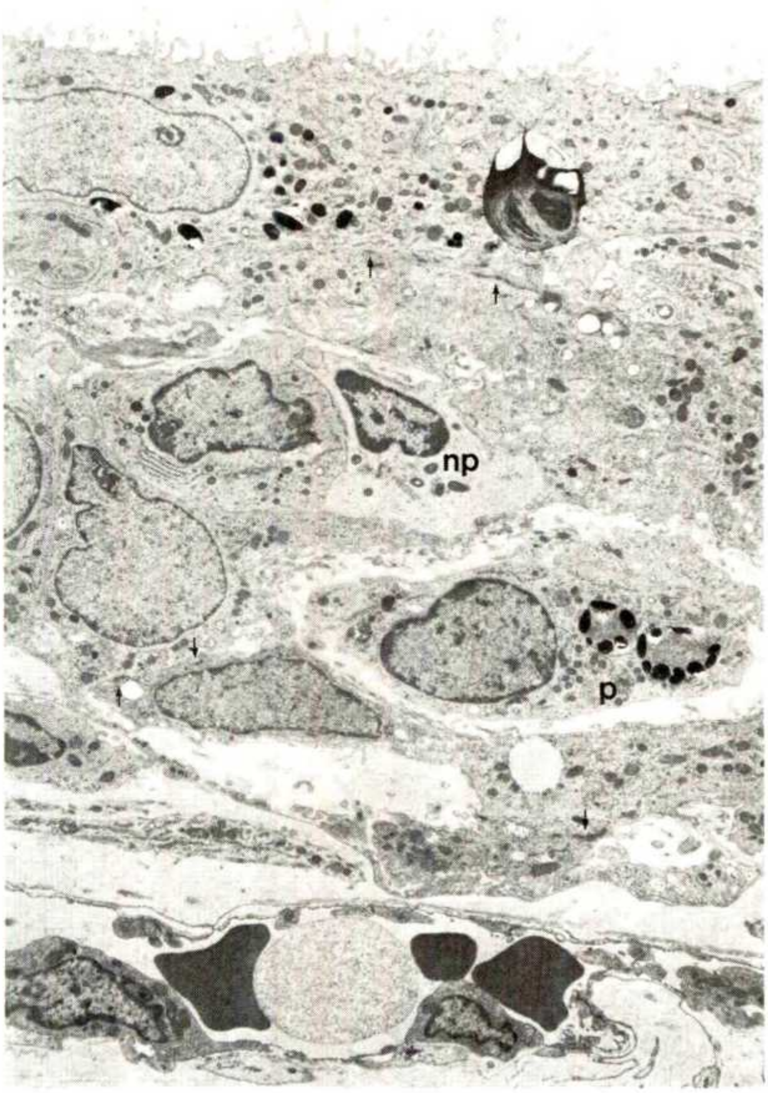


Fig. 11 *Electron micrograph of proliferated RPE showing tight framework of cells. Numerous cell junctions occur between the adjacent cells* (arrows). *Pigmented* (p) *and non-pigmented* (np). *Free cells occur among the framework of proliferated RPE* ×3040

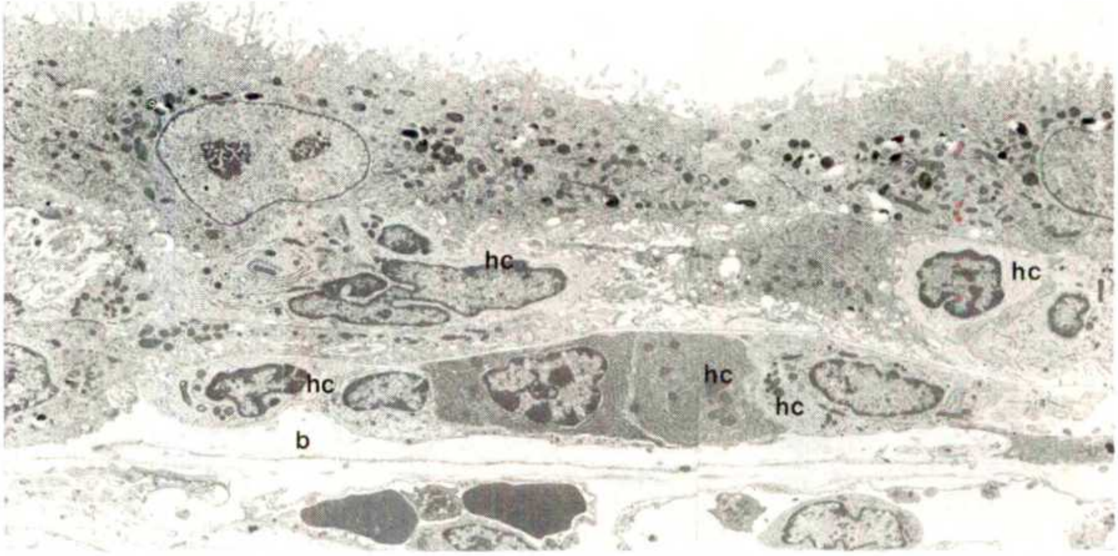


Fig. 12 *Electron micrograph of the RPE in an area of RPE proliferation showing thickening of Bruch's membrane* (b) *and free cells of haematogenous origin* (hc) *lying in Bruch's membrane or among the RPE cells* ×2790

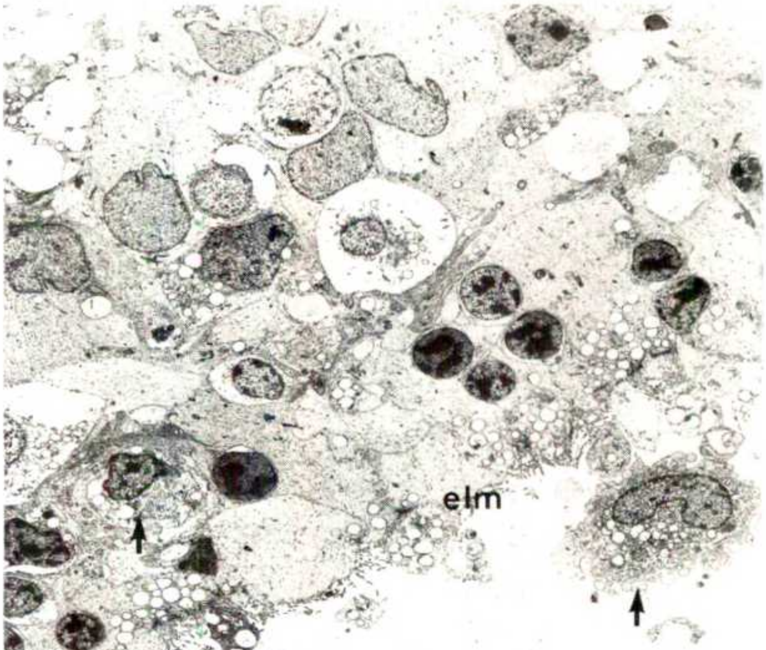


Fig. 13 *Electron micrograph of outer aspect of detached retina to show macrophage-like cells in the subretinal space underlying the external limiting membrane* (elm) *and intraretinally* (arrows) ×1200

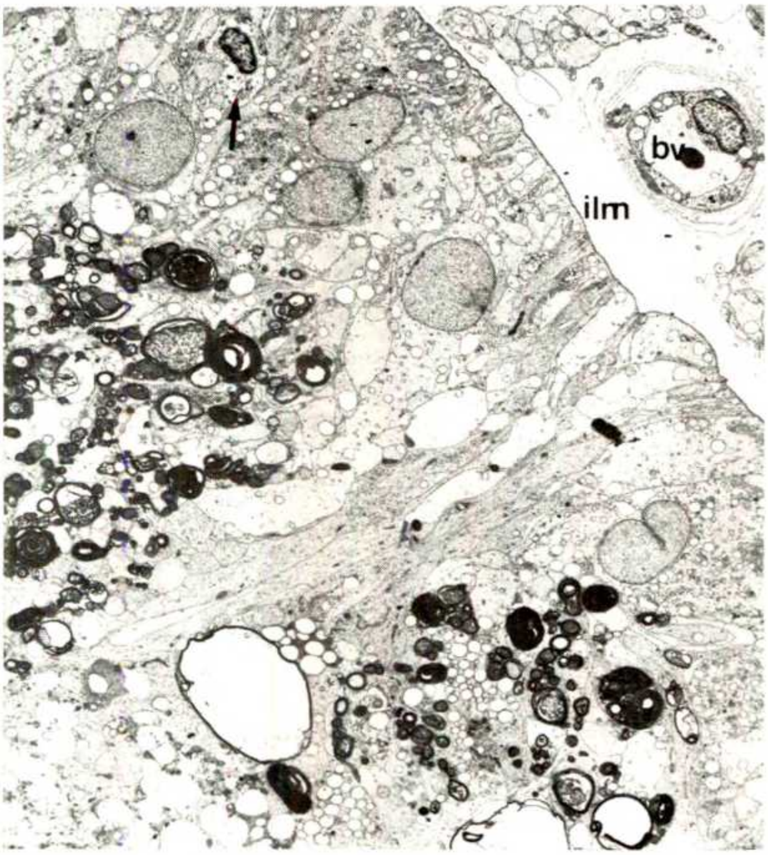


Fig. 14 *Inner aspect of detached retina shows normal extraretinal blood vessel* (bv), *intact internal limiting membrane* (ilm), *and macrophage-like cells within the retina* (arrow) ×1200

membrane free cells were found. Some of these cells contained melanin granules in the cytoplasm or in what appeared to be secondary lysosomal complexes. These cells had many characteristics of the RPE (Fig. 11) and were similar to the free cells already described as probably arising from RPE. The remaining free cells (Figs. 11 and 12) ranged from cells possessing a pale cytoplasm containing few organelles to cells with a more electron-dense cytoplasm containing prominent rough endoplasmic reticulum and Golgi apparatus. Within the thickened Bruch's membrane plasma cells were also found. These were generally located between the basement membrane of the RPE and the endothelium of the choriocapillaris (Fig. 12).

In addition to the changes seen in the RPE layer free macrophage-like cells were found in the subretinal space, underlying the external limiting membrane, and intraretinally (Figs. 13 and 14). These cells were generally without melanin granules and had a cytoplasm of low electron density.

The retinal blood vessels, which in the rabbit are largely superficial to the retina, appeared normal and showed no evidence of cell migration (Fig. 14).

Discussion

This study has shown that after experimental retinal detachment in the rabbit the RPE undergoes many morphological changes, some of which may represent the dynamic processes by which the RPE may give rise to macrophages which subsequently appear in the subretinal space and within the tissues of the detached retina. In regions where the RPE remains as a monocell layer this process appears to be the major source of retinal and subretinal macrophages.

Other possible origins for these macrophages include the circulating blood, for in areas where the RPE had proliferated to form a multicelled layer various cells of haematogenous origin and others not exactly classifiable could be seen within Bruch's membrane and between the proliferated RPE cells apparently making their way from the choriocapillaris through the RPE layer. Examination of the retinal vessels did not suggest migration of macrophages from the retinal capillaries, and it would appear that in areas where there is RPE proliferation Bruch's membrane and the proliferated RPE no longer pose a barrier to the inward migration of blood-borne cells.

Other theoretical sources of macrophages in detached retinae might be the retinal microglia or tissue histiocytes, but no evidence for either of these latter origins was seen in the tissue examined.

An unresolved problem is the fate of the residual cytoplasm of the RPE cell after the vitreal cytoplasmic protrusion has been 'nipped off' by adjacent cells. It was originally thought that the adjacent cells simply squeezed the intervening cells from Bruch's membrane, but on nearly every occasion there appeared to be a residual portion of the cell underlying the extensions of the adjacent cells. The question whether this cell fragment had a nucleus which was out of the plane of section is obviously of interest. The rabbit RPE has a high proportion (up to 80%) of binucleate and multinucleate cells (Tso and Friedman, 1967) and it may be that the residual cell fragment is indeed nucleated. No evidence for the further transformation of macrophages to fibroblasts was found in the tissues studied.

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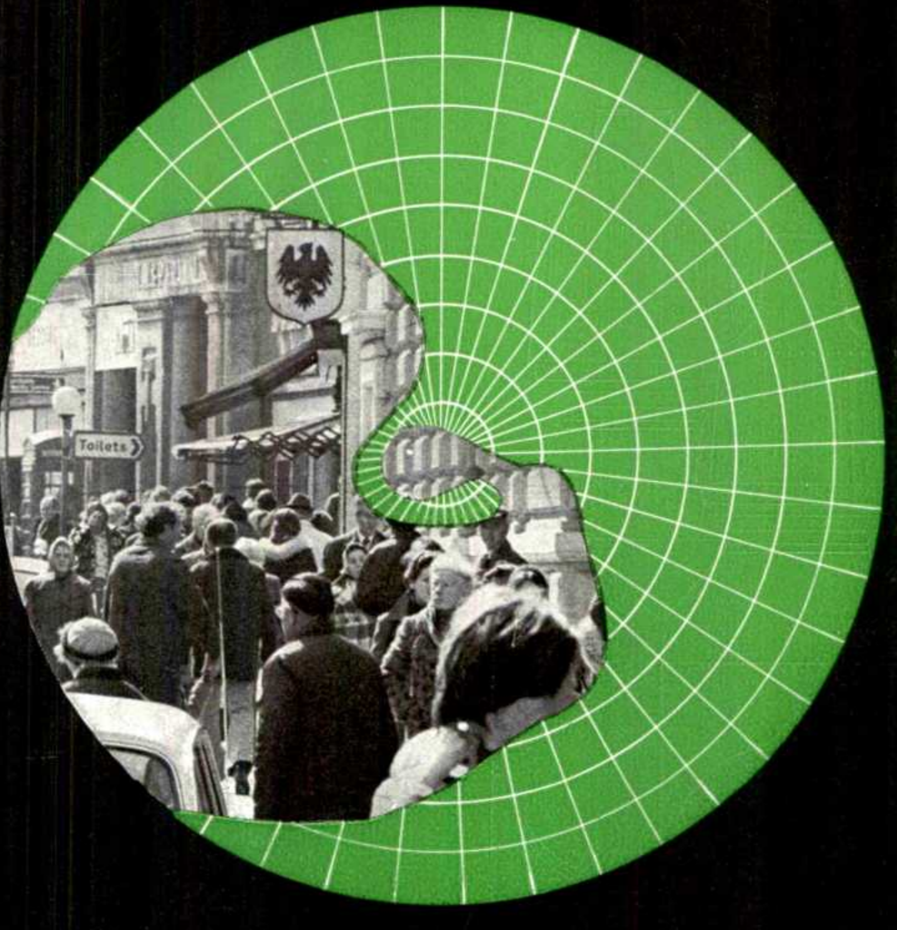

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Structural changes in the outer retinal layers following blunt mechanical non-perforating trauma to the globe: an experimental study

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SUMMARY Structural changes in the external retinal layers of pigs' eyes that had previously been subjected to blunt non-perforating mechanical injuries have been described. Within minutes of trauma fragmentation of the photoreceptor outer segments and damage to the retinal pigment epithelium was recorded in areas of retina adjacent to the missile impact site on the sclera. One week after injury the disrupted photoreceptor outer segments disappeared, and the inner segments came to lie adjacent to the retinal pigment epithelium. Evidence of regeneration of photoreceptor outer segments was noted 2 weeks later.

Disturbances of the retinal pigment epithelium are common sequelae to blunt ocular injuries in man, both at the posterior pole (Haab, 1888) and in the retinal periphery (Davidson, 1936). Few reports have appeared describing damage to the photoreceptors, though involvement of these cells might be expected owing to the intimate anatomical and biochemical relationship between the photoreceptor outer segments and the retinal pigment epithelium.

Absence of photoreceptors was recorded in a patient with a traumatic retinal detachment after a concussional ocular injury (Tillema, 1937), and more recently selective loss of these elements was reported in a patient who had recently sustained a blunt perforating ocular injury but did not develop a retinal detachment (Cogan, 1969). Disintegration of the external retina, with formation of vacuole-like cavities in the photoreceptor outer segment layer, was observed in the eyes of experimental animals (rabbits) examined less than 2 hours after being subjected to blunt non-perforating mechanical trauma (Petropavlovskaya and Bogoslovsky, 1966).

Damage to the outer retinal layers following blunt non-perforating mechanical injuries has been attributed to concussional forces: (1) Producing spasm of the choroidal circulation (Bonnet and Sedan, 1954) leading to ischaemic tissue necrosis; (2) acting on the retinal epithelial cells to induce these to become mobile phagocytes, which digest the adjacent layers of the retina (Cogan, 1969); (3) by disrupting the pigment epithelium, causing lysosomal liberation with the same end result as above (Cogan, 1969).

Since opportunities to examine microscopically any cellular changes which occur after concussional injuries to the human retina rarely arise, especially within a few days of the event, the eyes of experimental animals (pigs) were subjected to blunt traumatic injury. At predetermined times the globes were removed and examined histologically.

Materials and methods

EXPERIMENTAL ANIMALS

All trauma experiments were performed on 20-kg store pigs. The pig was selected because this animal has a holangiotic retinal blood supply with a capillary meshwork of about the same size, and supplying identical retinal layers, as the human (Rootman, 1971). The eyeball dimensions are similar to those of man, thus the forces liberated by a missile impacting against the globe might be expected to act on the intraocular tissues in a somewhat similar way.

TRAUMA

This was produced by firing a pellet from a modified airgun to give a missile impact energy of approximately 0·56 ft lb (0·08 kg m). At this energy level ocular perforation did not occur (Weidenthal and Schepens, 1966). The slug was made to impact perpendicularly against the sclera in the 3 o'clock

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position in the right eye and in the 9 o'clock position in the left eye, 4 to 5 mm from the corneoscleral junction.

ANAESTHESIA

All experiments involving ocular trauma were performed under general anaesthesia. This was induced and maintained by the animal breathing a mixture of fluorothane in nitrous oxide and oxygen on open circuit, delivered through a flexible rubber nose cone which fitted over the animal's snout. No additional premedication was used.

LIGHT AND ELECTRON MICROSCOPY

Eyes were carefully but quickly enucleated prior to killing the animal. Seven animals formed the basis of this investigation and the globes were removed at the following time intervals after trauma: within 1 minute, at 1 day, 7 days, 3 weeks, and 2 months.

After removal of the eye a wide incision was made through the ocular coats in the region of the pars plana with a dermatome blade, and the globe was immediately placed in 150 ml of solution at 4°C containing 4% glutaraldehyde buffered with 0·6 M sodium cacodylate to give a pH of 7·4. After 15 minutes' initial fixation the incision was completed and the posterior eye cup returned to the fixative. Two hours later the posterior cup was transferred to cold 0·5 M sucrose solution buffered with 0·2 M sodium cacodylate, and 5 mm discs of full-thickness retina, choroid, and sclera were trephined out of selected areas of the retina. These included samples from the mid-nasal and mid-temporal regions and were taken along a horizontal plane which passed through the point of impaction of the missile.

Tissue was post-fixed in Millonig's phosphate buffered osmium tetroxide for 1½ hours. After dehydration in ascending concentrations of ethanol the samples were embedded in Spurr resin and sections cut on a Reichert OMU 2 ultramicrotome. Thick sections at 0·5 μm were stained with toluidine blue for photomicrography with Nomarski differential interference contrast. Thin sections were cut, mounted on copper grids, stained with uranyl acetate and lead citrate, and examined with the Phillips EM300 electron microscope.

Results

Changes in the outer retinal layers of eyes removed within 1 minute of trauma

An interference contrast photomicrograph shows the normal appearance of a pig's external retinal layers (Fig. 1). Immediately after trauma fragmentation of the photoreceptor outer segments occurred in the nasal retina adjacent to the site of missile impact on the outer coats of the globe, but no loss of continuity of the retinal pigment epithelial layer or ruptures of Bruch's membrane developed. Occasional haemorrhages were present in the outer retinal layers, but the choroidal vessels appeared to be everywhere intact (Fig. 2). When compared with its appearance in Fig. 1, the outer limiting membrane showed no evidence of dehiscences or breaks.

Electron micrographs of the nasal retina also show that marked disruption of the photoreceptor outer segments had occurred. The fragments consisted of irregular-sized pieces recognisable as outer segment material containing 20 or more saccules and as loose skeins of disc plates. The photoreceptor inner segments appeared to be somewhat separated from each other, but the severity of damage to these structures was less marked than in the outer segments, and only a few of the cell boundaries were ruptured. Cleavage of the outer from the inner segments of the photoreceptors had occurred mainly at the level of the connecting cilia (Fig. 3). The tips of the outer segments of the photoreceptors had, with few exceptions, lost contact with the retinal pigment epithelium. Only the occasional apical process could be identified, and there was evidence of some ruptures in the retinal pigment epithelial inner cell membranes, as pigment cell particles could be observed in the area occupied by the fragmented outer photoreceptor segments. However, the outer and lateral cell boundaries, including the junctional complexes of the retinal pigment epithelial layer, appeared to be intact. Intracellular oedema of the retinal pigment epithelial cells was an obvious feature, and numerous microcystic spaces were present. Phagosomes were detected at this stage after trauma. Bruch's membrane and the choroidal vessels showed no evidence of damage, either immediately after injury or at later stages (Fig. 4).

Electron micrographs of sections obtained from the temporal retina on the opposite side of the globe to where the airgun pellet had struck the eye reveal no evidence of structural damage in the outer retinal layers (Fig. 5).

Microscopical appearances of the outer retinal layers of eyes removed 24 hours after trauma

Electron micrographs obtained from sections of the nasal retina showed that the fragments of lamellar disc material were less electron-dense than 24 hours previously, and the discrete fragments containing saccules had almost disappeared. Retinal pigment epithelial cells showed more evident intracellular oedema as the inner cell boundaries had become ballooned out. Few apical processes could be detected, and no phagosomes were observed. Isolated wandering macrophages containing electron-dense

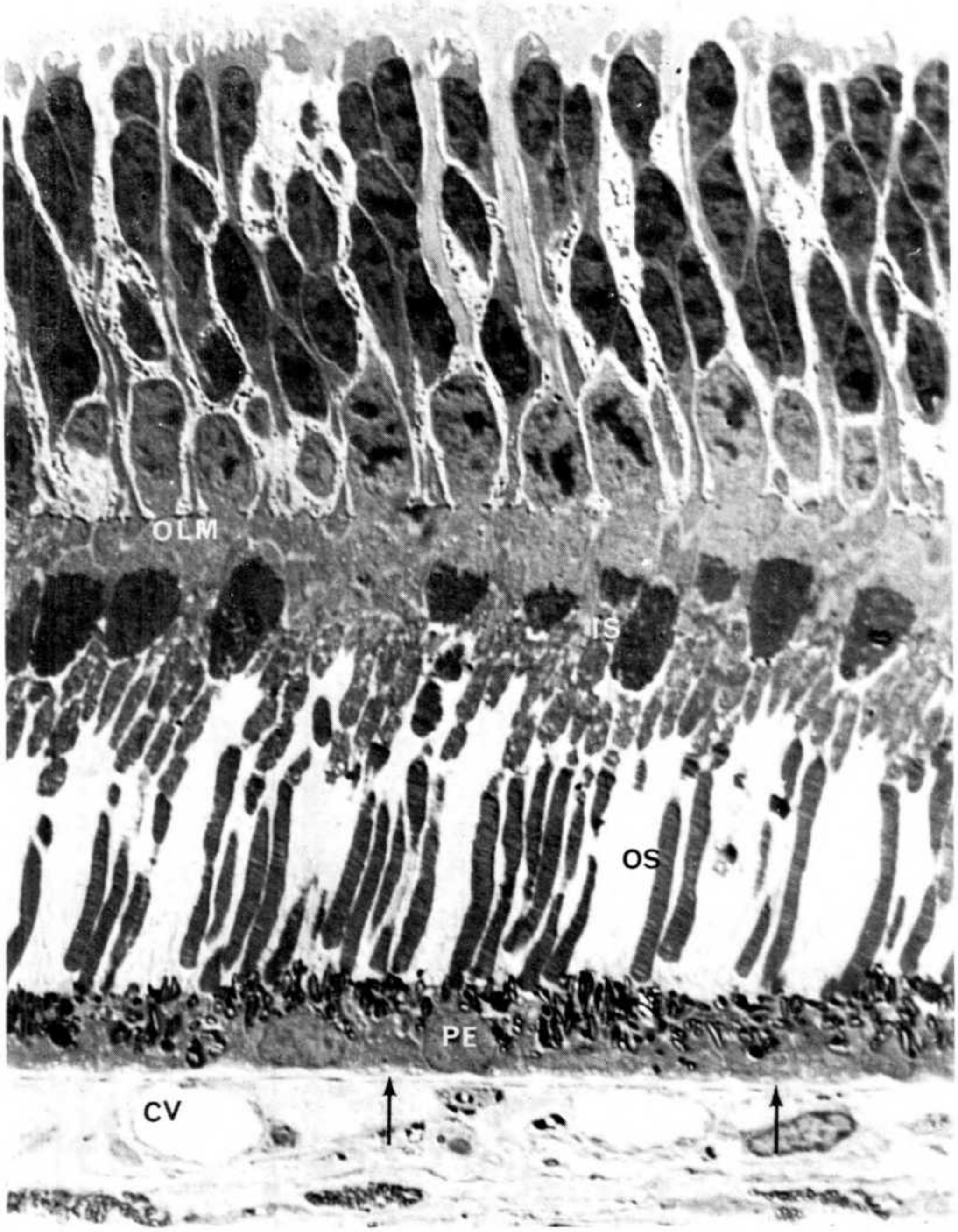

Fig. 1 *Interference contrast micrograph of untraumatised retina. Outer limiting membrane, OLM: photoreceptor inner segments, IS: pigment epithelium, PE: Bruch's membrane* (arrows): *choroidal vessels, CV.* ×1640

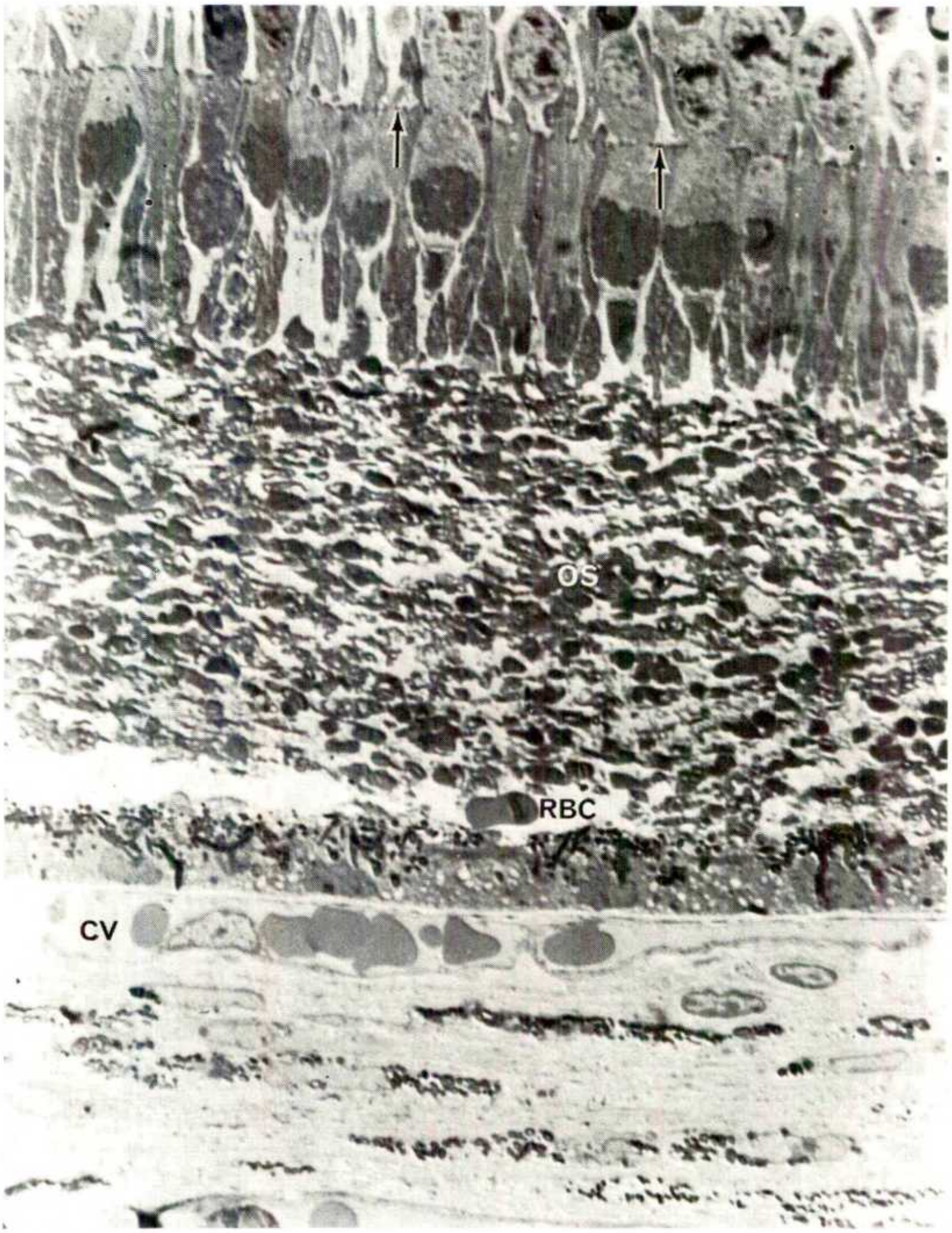

Fig. 2 *Interference contrast micrograph of nasal retina of globe removed within 1 minute of trauma, showing disruption of the outer segment layer, OS. No breaks are present in the outer limiting membrane* (arrows) *or the pigment epithelium. Occasional haemorrhages, RBC, can be identified, but the choroidal vessels, CV, appear intact.* ×1640

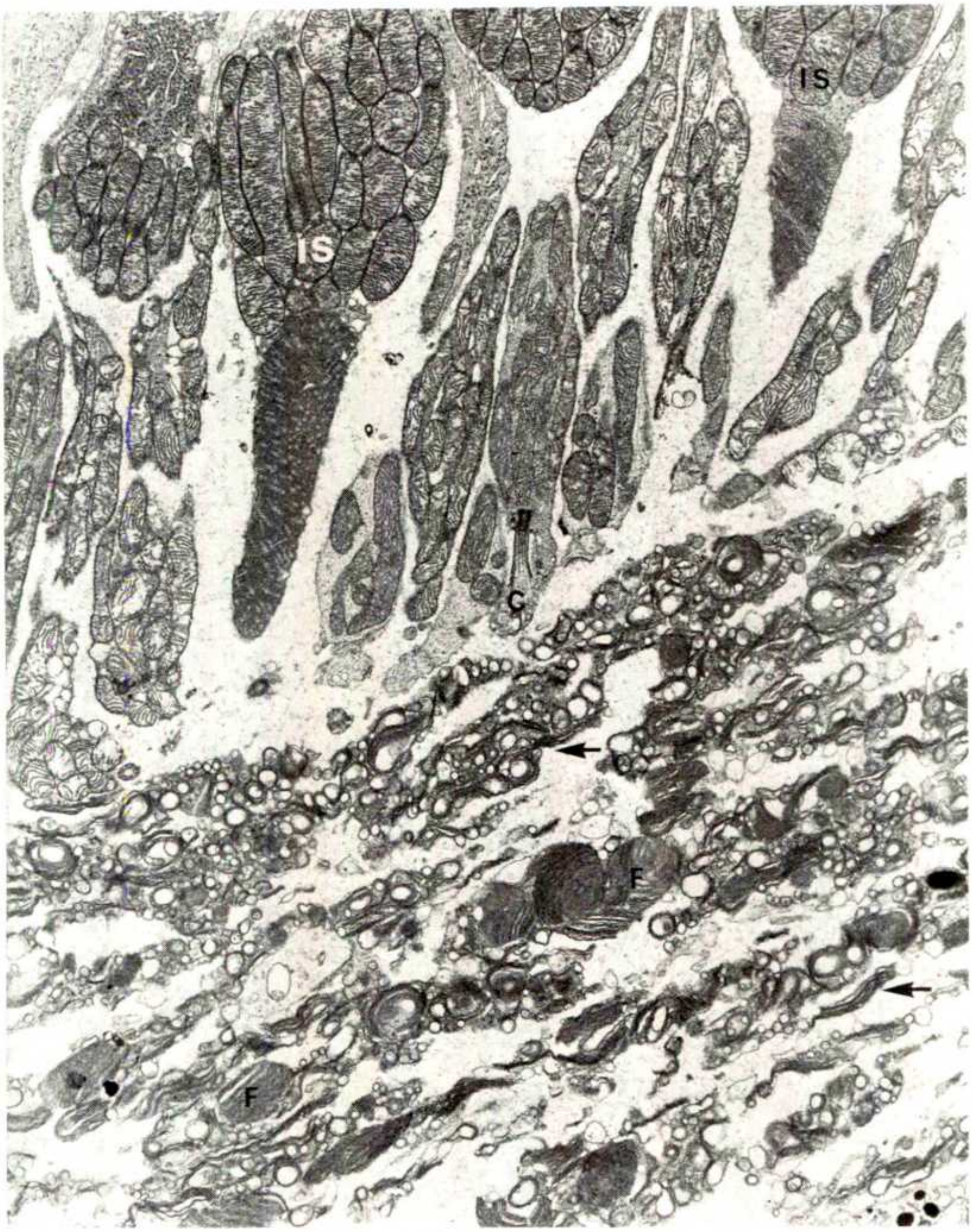

Fig. 3 *Electron micrograph of nasal retina of globe removed within 1 minute of trauma, showing fragmented outer segment material consisting of loose discs* (arrows), *and fragments containing saccules, F. Inner segments, IS, are separated from each other, but show less damage than outer segments, which have split off at the level of the connecting cilia, C.* × 6900

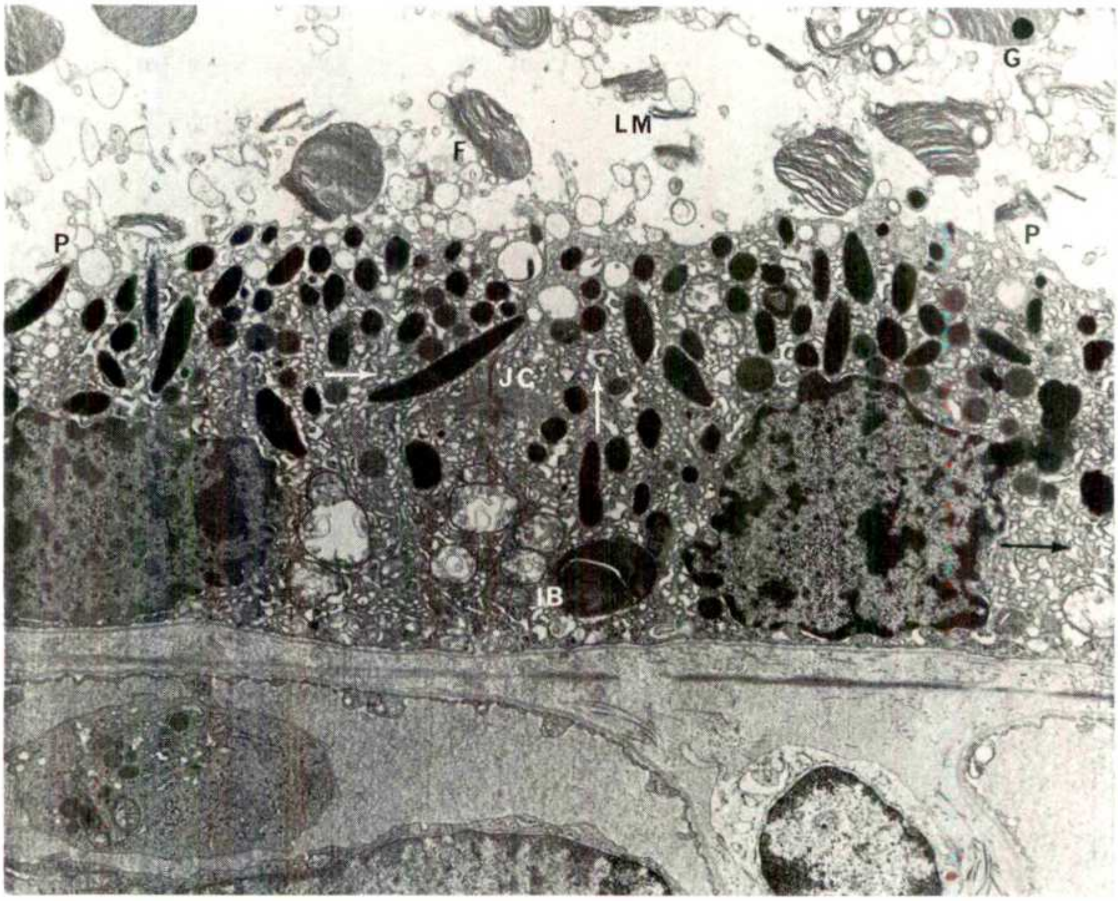

Fig. 4 *Electron micrograph of nasal retina of globe removed within 1 minute of trauma. There are numerous microcystic spaces in the cytoplasm of the pigment epithelium* (arrows). *A few stunted apical processes, P, can be seen, and some inner cell membranes have ruptured with dispersion of pigment granules, G. The lateral and outer cell boundaries are intact, including the junctional complexes, JC. Lamellar inclusion bodies, IB, are present. Fragmented outer segments consist of loose lamellar material, LM, and fragments containing saccules, F.* ×8680

material derived from the pigment epithelium were seen only in the occasional section (Fig. 6).

Sections of the outer retinal layers obtained from the temporal retina failed to demonstrate any abnormal features.

Microscopical appearances of the outer retinal layers of eyes removed 7 days after trauma

Interference contrast micrographs of the nasal retina show that the photoreceptor inner segments had become approximated to the inner cell boundaries of the pigment epithelium. The space which contained the fragmented photoreceptors had disappeared (Fig. 7).

Electron micrographs confirm that the layer previously occupied by the photoreceptor outer segments had collapsed and the cell debris dispersed. Only a few stumps of outer segment material were identifiable, which were possibly regenerating photoreceptor outer segments (see below). The retinal pigment epithelium appeared to be less swollen, and apical processes were again observed in large numbers (Fig. 8). No phagocytic activity could be detected by the presence of wandering macrophages, and no phagosomes were seen within the pigment epithelial cells. Sections obtained from the temporal retina appeared free of structural changes.

Microscopical appearances of the outer retinal layers of eyes removed 3 weeks after trauma

Interference contrast micrographs of the nasal retina show that the outer segments had reappeared (Fig. 9).

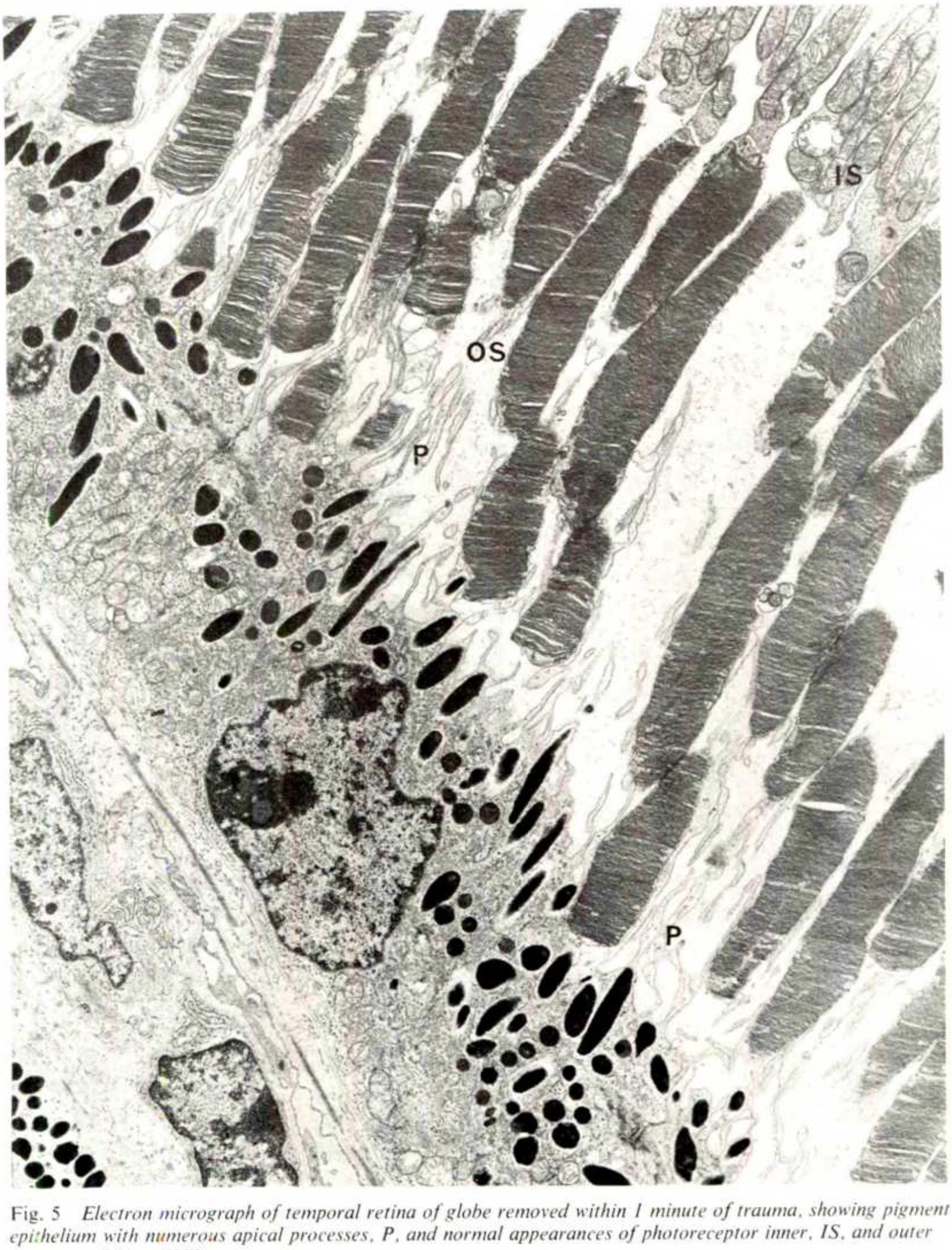

Fig. 5 *Electron micrograph of temporal retina of globe removed within 1 minute of trauma, showing pigment epithelium with numerous apical processes, P, and normal appearances of photoreceptor inner, IS, and outer segments, OS.* × 6900

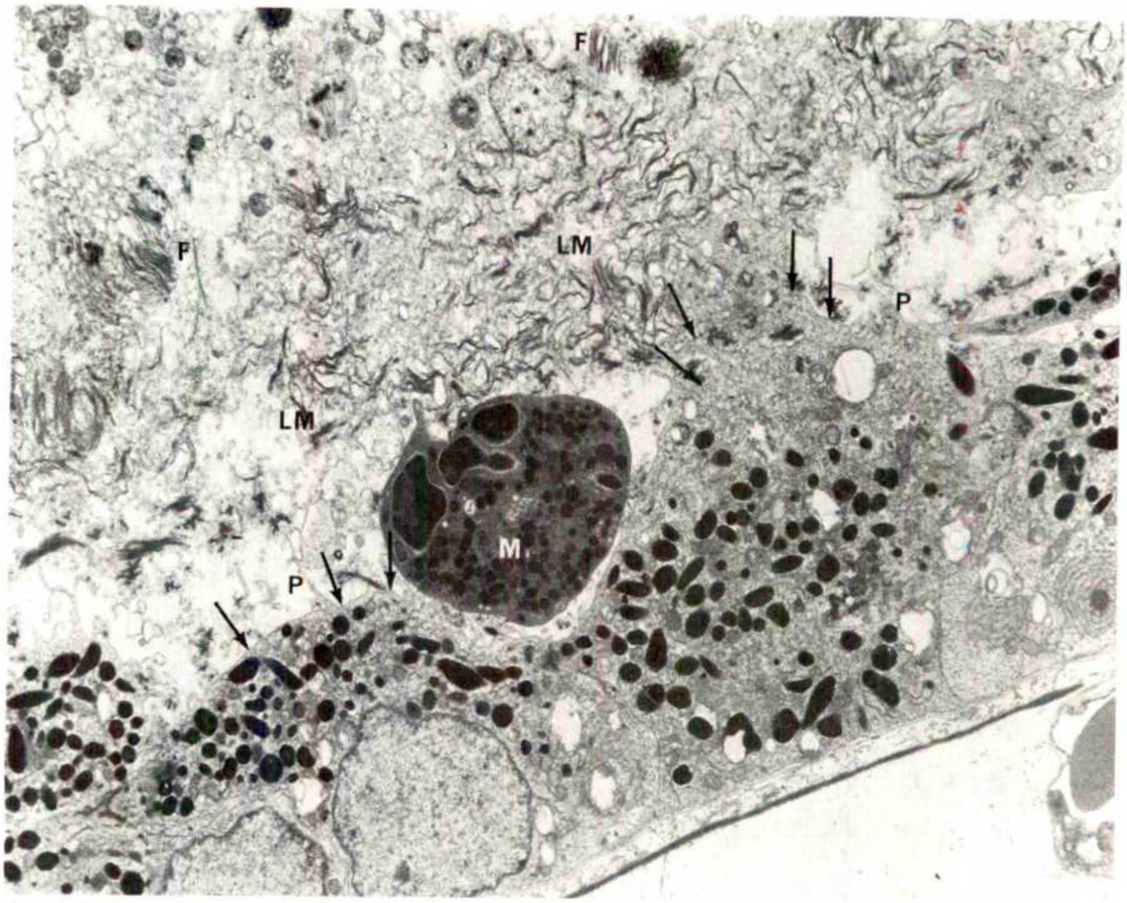

Fig. 6 *Electron micrograph of nasal retina of eye removed 1 day after trauma. There is ballooning of the pigment epithelium inner cell membrane* (arrows), *and few apical processes, P, can be identified. Loose disc material, LM, is less electron-dense than 24 hours previously and few fragment containing saccules, F, remain. The occasional macrophage, M, containing pigment material is present.* × 5960

Electron micrographs show that a complex pattern of changes had occurred in the outer retinal zones. There was evidence of regeneration of outer segment material, some of which was fairly orderly and some extremely disorganised. Lamellar material in some outer segments had been produced in the form of whorls surrounding clear central spaces, as ribbon-like streamers and, in some cells, was present in the inner segment (Fig. 10). In other outer segments cystic spaces could be seen between the saccules, abnormal orientation of disc plates was evident in the tips of the processes, and large portions of the outer segments were filled with amorphous ground material (Fig. 11). Many saccules were stunted. Phagosomes were again noted in the pigment epithelial cells. Studies of the outer layers of the temporal retina showed no abnormal features.

Microscopical studies of outer retinal layers of eyes removed 2 months after trauma

Electron micrographs of nasal retina show that the production of outer segment material had now developed along more normal lines and that, in the majority of the outer segments, saccules were correctly orientated. The tips of the photoreceptor outer segments had established a normal relationship with the pigment epithelial cells, but in a few photoreceptors disorganised production of lamellar plate material continued (Fig. 12).

Discussion

Selective loss of photoreceptor outer segments has been reported in man following detachments secondary to malignant tumours (Kroll, 1969), and

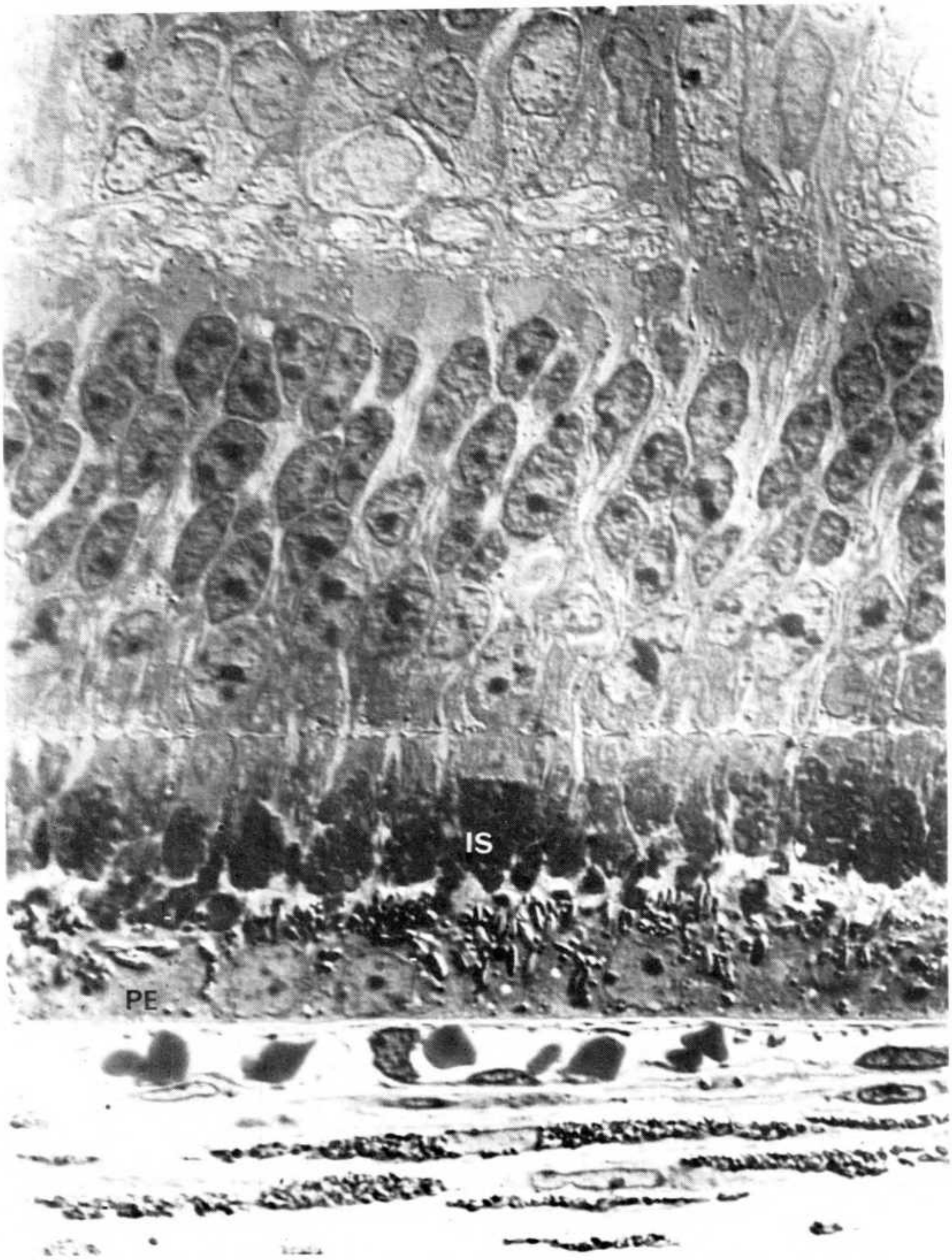

Fig. 7 *Interference contrast micrograph of nasal retina of eye removed 1 week after trauma, showing approximation of inner segment, IS, to the pigment epithelium, PE.* × 1640

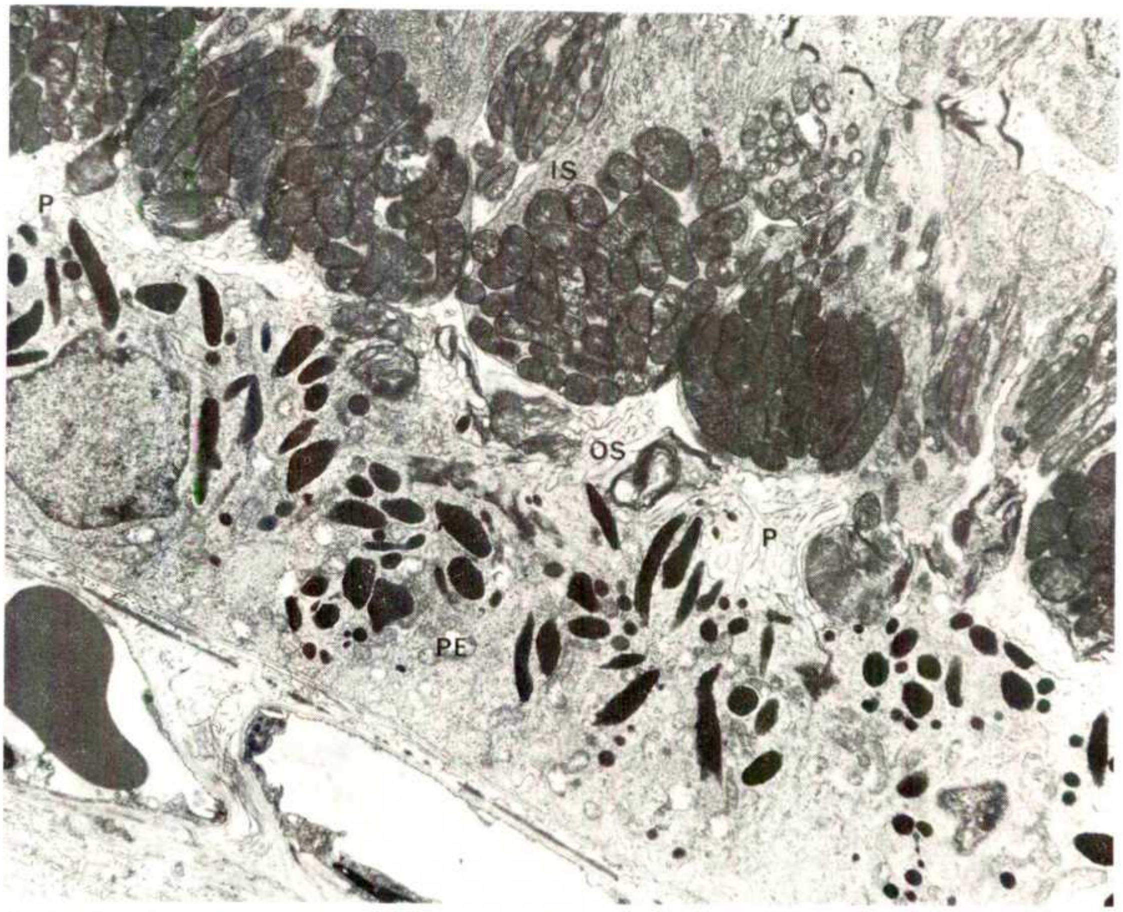

Fig. 8 *Electron micrograph of nasal retina of eye removed 1 week after trauma. The zone previously containing fragmented outer segment material is almost obliterated. The inner segments, IS, lie adjacent to the pigment epithelium, PE. Only a few pieces of outer segment material, OS, are present. Apical processes, P, are seen in large numbers.* ×5960

studies on animals with experimental retinal detachments showed that these structures gradually atrophied (Kroll and Machemer, 1968). It is possible that the absence of photoreceptors noted in patients with traumatic detachments of the retina (Tillema, 1937; Crouch and Apple, 1974) occurred, in part, because contact between the outer segments and the retinal pigment epithelium was lost.

In this study marked outer retinal layer cellular changes were immediately apparent after trauma. They appeared too early for ischaemia, as suggested by Bonnet and Sedan (1954), or a breakdown in the biochemical pathways between the photoreceptors and retinal pigment epithelial cells to have played a major part in producing them. Examination of the choroidal vasculature did not reveal any evidence of vessel damage either immediately after trauma or for periods of up to 2 months after the injury.

We have previously described disturbances of the nerve fibre layer of the retina in experimental animals after blunt non-perforating mechanical trauma (Hart *et al.*, 1975) that could have resulted only from forces released at the time of missile impaction acting directly on the cellular elements of the retina. The present findings of immediate fragmentation of the photoreceptor outer segments, with separation of these structures from the inner segments at the level of the connecting cilia, loss of the apical processes of the retinal pigment epithelium, and intracellular oedema of these cells after injury can only be attributed to similar causes.

No ruptures of the junctional complexes were noted on microscopy between adjacent retinal pigment epithelial cells or at the level of the outer

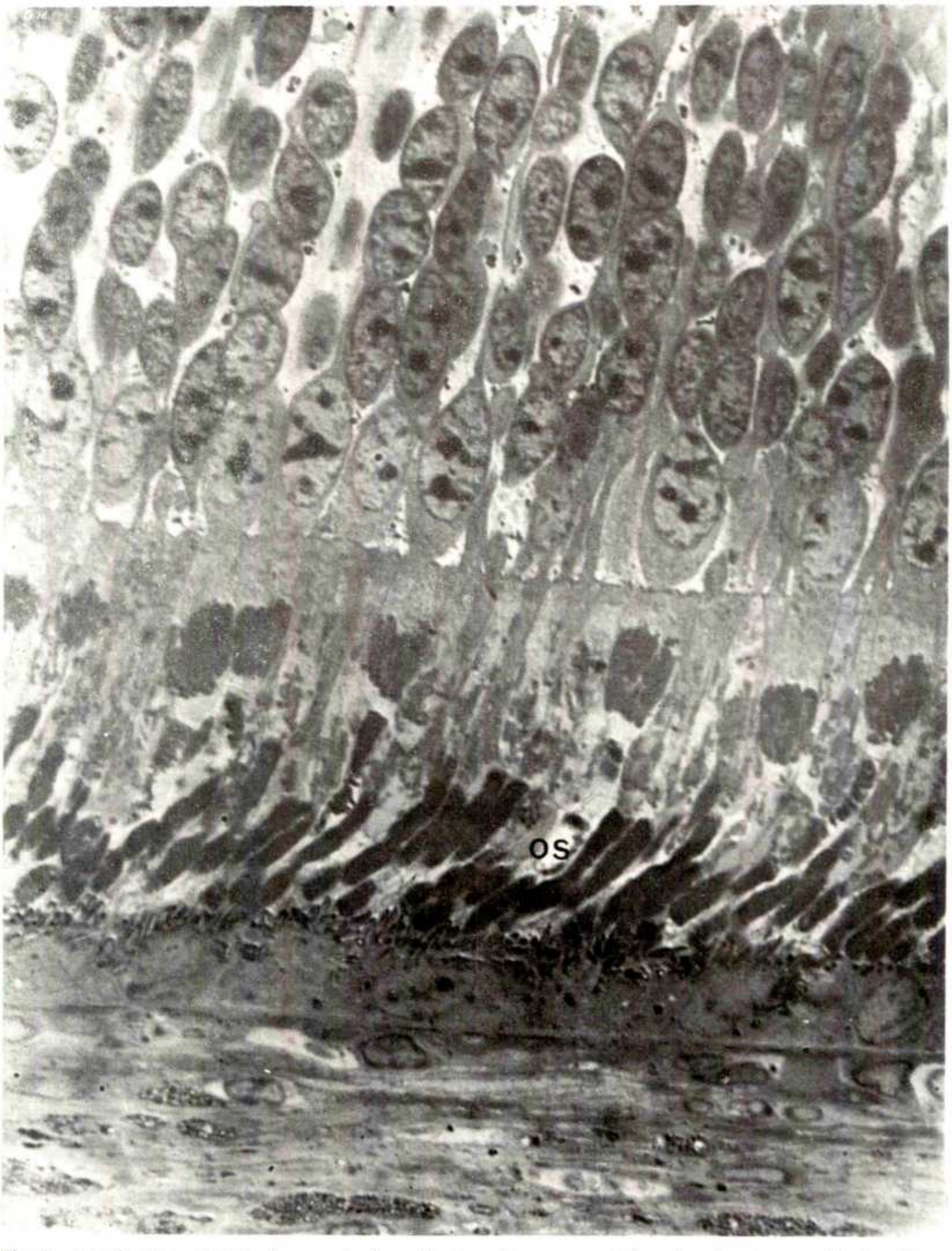

Fig. 9 *Interference contrast micrograph of nasal retina of eye removed 3 weeks after trauma, showing the presence of stunted outer segments, OS.* ×1640

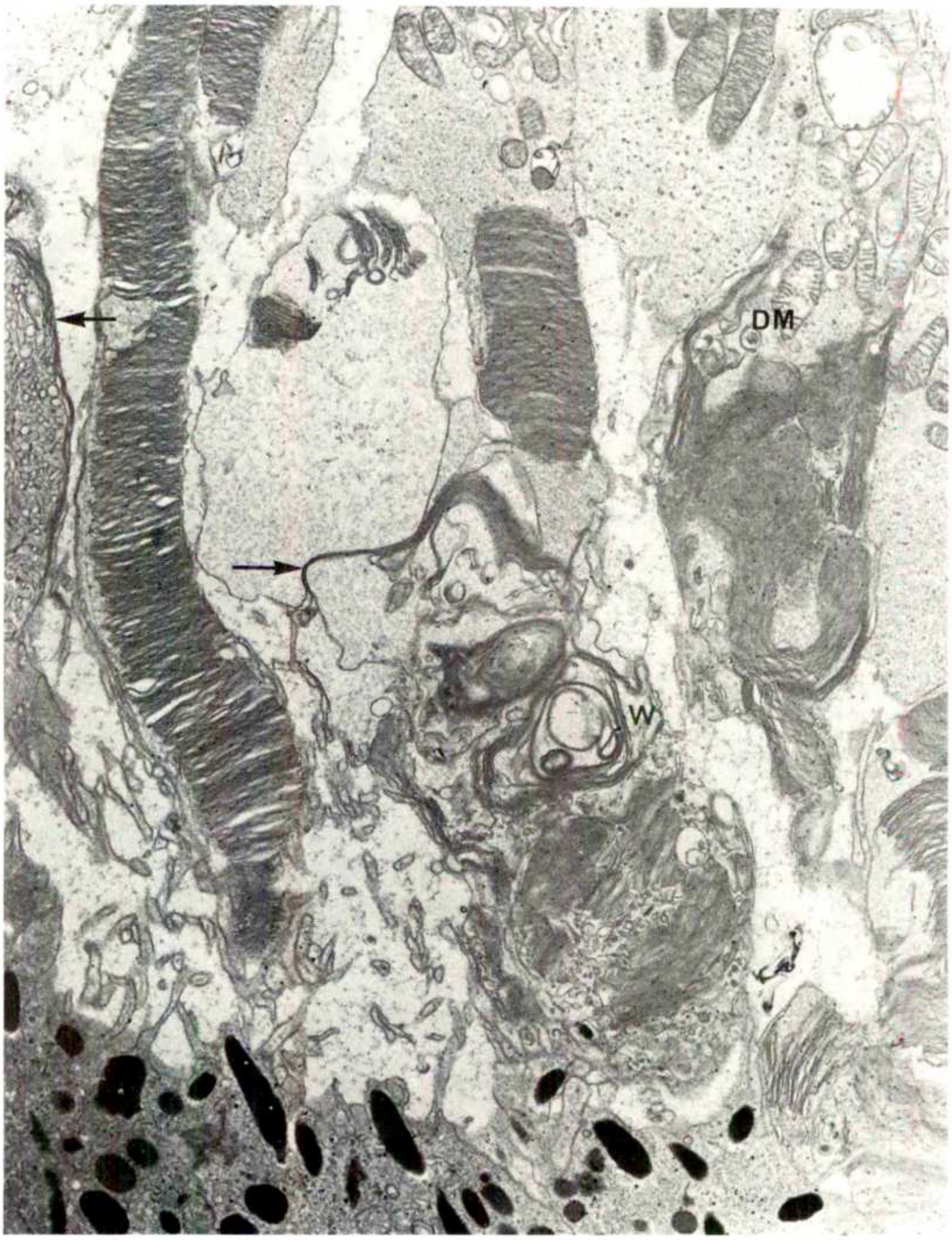

Fig. 10 *Electron micrograph of nasal retina of eye removed 3 weeks after trauma, showing abnormal appearances of outer segments with whorls of plate material, W, surrounding cystic spaces, ribbon-like strands* (arrows), *and disc material, DM, being produced in the inner segments.* ×11 100

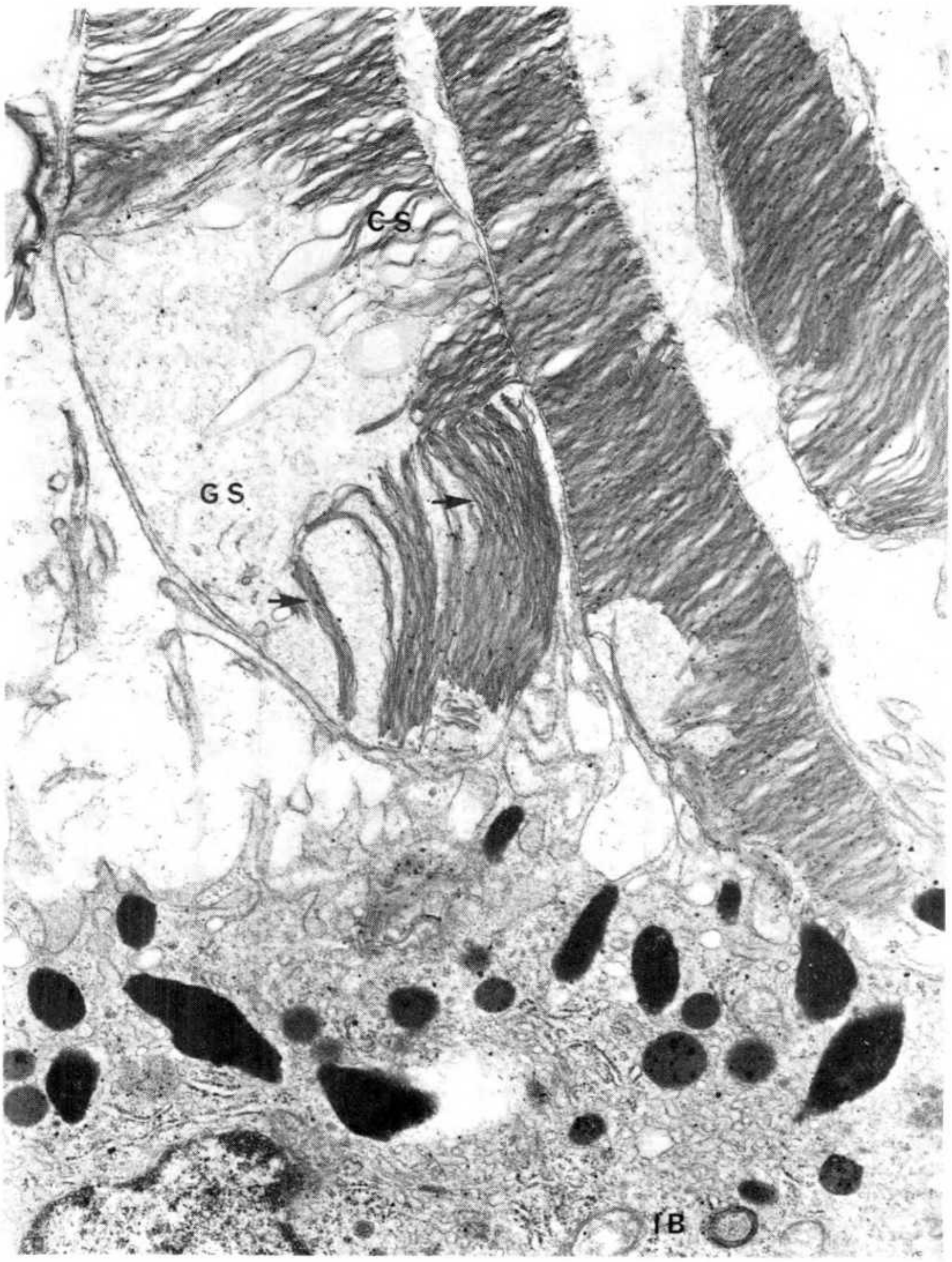

Fig. 11 *Electron micrograph of nasal retina of eye removed 3 weeks after trauma, showing regenerating outer segments with cystic spaces, CS, between saccules, vertically orientated discs* (arrows), *and outer segments containing large quantities of amorphous ground substance, GS. Lamellar inclusion body, IB.* ×18 500

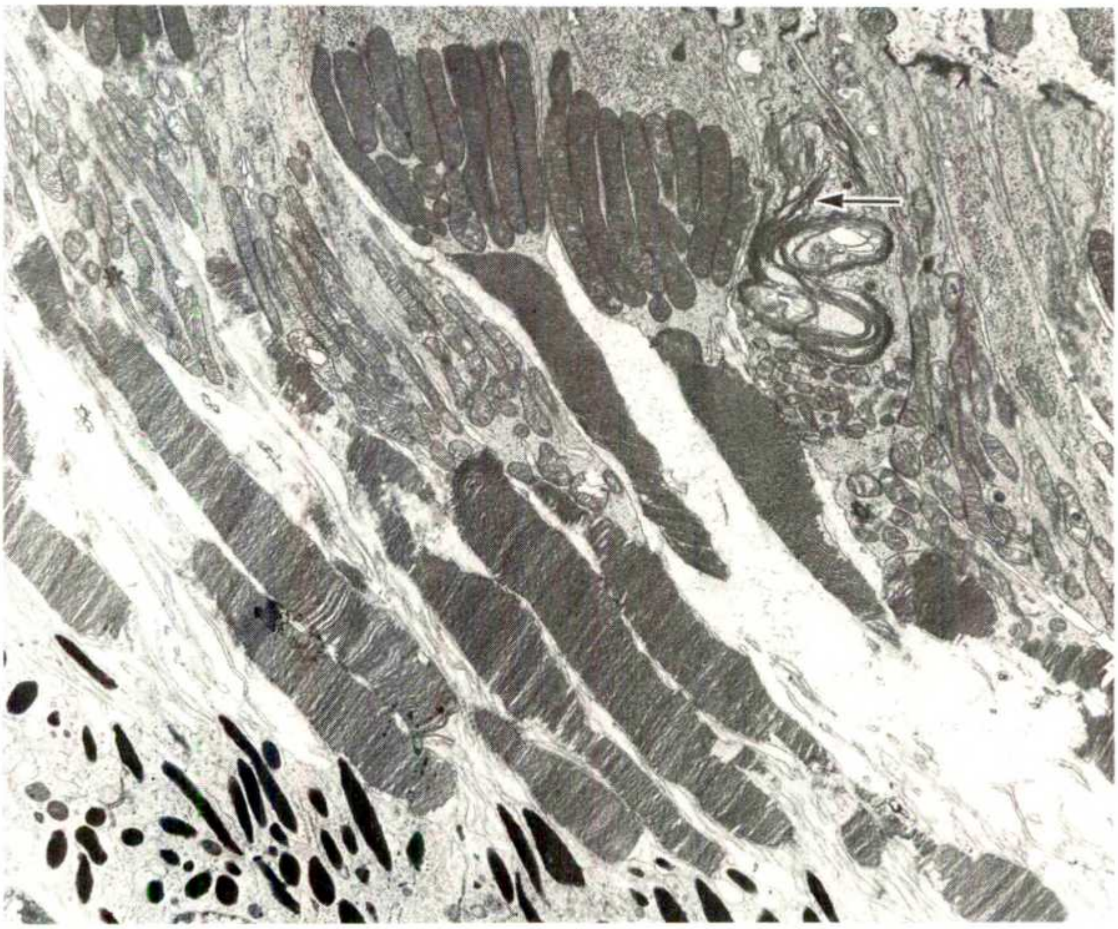

Fig. 12 *Electron micrograph of nasal retina of eye removed 2 months after trauma. More normal looking photoreceptor outer segments. Some disordered regeneration of disc material is seen in the inner segment* (arrow). ×6585

limiting membrane after trauma. These structures may perhaps play some role in resisting distracting forces, thereby permitting shearing stresses to act only at certain levels of the retina.

Changes in the outer layers of the retina were maximal adjacent to the impact site and declined away from this point. No signs of contre-coup injuries were detected, thus supporting the *in-vitro* findings on pigs' eyes of Delori *et al.* (1969) that the forces generated by missiles of relatively high velocity and low mass impacting against the globe are transmitted via the ocular coats and not as block forces across the vitreous gel.

Repair of the pig's retinal pigment epithelium occurred quickly after trauma; the internal cell membrane was reconstituted and the apical processes reappeared within 7 days of injury. However, the dramatic disappearance of the fragmented outer segments within 1 week of trauma, with approximation of the inner segments of the photoreceptors to the retinal pigment epithelium, almost certainly did not come about as a result of phagocytosis by wandering macrophages, since very few of these cells were observed in our sections. It is possible that after trauma to the pig's retina enzymes released either from outer segments or from the damaged retinal pigment epithelium digested the disrupted outer segments *in situ,* a mechanism suggested by Cogan (1969) to explain similar changes which have been noted in man, and that the products of this process then rapidly diffused away into the surrounding tissues.

Regeneration of the outer segments, which was initially grossly disordered and characterised by the production of long streamers of lamellar material, incorrectly orientated plates, and whorl-like formations, some of which appeared to be formed in the inner segments, but becoming more orderly subsequently, has been reported after the reattachment of experimentally detached retinae (Kroll and Machemer, 1969). Since photoreceptor regeneration also occurs after blunt non-perforating mechanical injuries in pigs, it would appear that some elements of visual function may continue to improve over a period of weeks after blunt non perforating injuries in these animals.

The amount of pigment dispersion detected within the retina 2 months after trauma in pigs was minimal, both on ophthalmoscopic and on microscopical examination. It is possible that in this animal the retinal pigment epithelium shows a higher degree of stability to such injuries than in some other species, including man.

The degree of retinal damage which follows concussional injuries depends on the magnitude of the stresses imposed on this tissue. Traumatic retinal oedema, as described by Berlin (1873) is rapidly reversible, and Berlin stressed that retinal function quickly returns to a preinjury level. Experimental studies suggest that retinal opacification probably occurs in such cases because of the development of intracellular oedema at the level of the nerve fibre layer (Hart *et al.*, 1975).

Fluorescein angiographic studies performed on patients presenting with Berlin's oedema showed no abnormal features, but in a patient who later developed retinal pigment epithelial disturbances visible on ophthalmoscopic examination fluorography performed soon after trauma revealed a temporary breakdown of the choroido-retinal barrier, with pooling of dye in the neural layers of the retina (Hart and Frank, 1975). In this case, with clear evidence of post-traumatic damage to the outer layers of the retina, central vision was initially severely impaired but continued to improve for several weeks, although no refractive error or loss of clarity of the optical media was present more than 4 days after trauma. The possibility exists that regeneration of disrupted photoreceptor outer segments noted in the retinae of pigs after concussive injuries may also, in favourable circumstances, occur in man.

We wish to thank Mr P. Darby for technical assistance and Mrs M. Roach for secretarial services.

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Retinal detachment treated with intravitreal air: an evaluation of 241 cases

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SUMMARY 241 unselected cases of retinal detachment treated since 1971 with cryopexy and intravitreal air are discussed. The series is analysed according to the position of the retinal tear(s), and we describe briefly the surgical technique and evaluate the main complications.

The unchanging aim of retinal surgery is to reattach a living retina with as little damage to it and the rest of the eye as is consistent with success—at a first operation. There are many methods of achieving this end, and all retinal surgeons have been forced by the demands of different cases to use most of them at one time or another. It is only when the surgeon is left with a choice that any controversy occurs.

Methods

The use of intravitreal air has already been described in detail (Chawla and Birchall, 1973; Chawla, 1974). The basic operation may be briefly summarised here. Monitored freezing is applied to the retinal break(s); subretinal fluid is released through a scratch sclerotomy over a carefully selected site; sterile air is injected into the vitreous through the pars plana; a fine silicone band (No. 40) is placed around the equator of the eye; the patient is then positioned postoperatively to float the break(s) uppermost against the frozen area(s) for at least 48 hours. Two variations from the original technique should be mentioned.

SUBRETINAL FLUID

Before piercing the choroidal knuckle we now first coagulate it with a round ball diathermy electrode in the manner advocated by Freeman and Schepens (1974) though without any transillumination.

LOWER TEAR(S)

All except large equatorial breaks, lying between the 5 and 7 o'clock meridians, are treatable with intravitreal air. To raise the lower pole of the eye uppermost the patient is nursed head downwards in a tilted bed with a stitch around the inferior rectus muscle for 24 to 48 hours (see Fig. 1). Two main considerations determine whether patients are suitable for this method of treatment: (1) It must be possible to float the tear(s) uppermost; (2) the eye must be softened enough to make room for at least 1 ml of intravitreal air. This is usually done by subretinal fluid release, hence we prefer balloon to shallow detachments, but it may be necessary to alter the volume with intravenous mannitol solution or in rarer cases by release of fluid vitreous along a Graefe blade through the pars plana (Fig. 2).

AUGMENTED OPERATION

Where tears are present in opposite quadrants, not treatable with a single air bubble, we have sealed the lower tear with a radial sponge implant on the equator or with a circumferential segment of guttered silicone band (No. 20) for peripheral break(s). Local counter-traction is sometimes needed in the presence of a rigid retina, either as a primary or as a secondary procedure.

Although Rosengren (1938) had already established vitreal air injection as a reputable method, we were reluctant at first to use it freely. However, its effective simplicity, speed, and freedom from complications have now persuaded us to give it a rapidly increasing share (now 90%) of the retinal detachments treated in our service. Because of this earlier hesitation, the 241 cases discussed in this paper form less than 50% of our total numbers since 1971, but with 200 detachments per year to treat, it is now our procedure of choice. In this present group of patients the shortest follow-up is 6 months at the time of writing.

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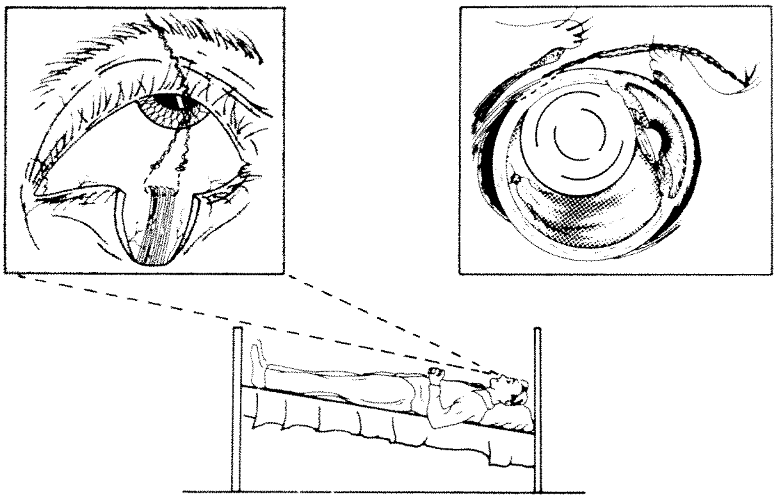

Fig. 1 *Inferior rectus stitch. Tilted bed*

We have broken the cases up according to the position and nature of the retinal tear(s), taking a flat retina as our main criterion of success but not dismissing the influence that the preoperative state of the macula and vitreous has had on central visual recovery (Chisholm *et al.*, 1975).

EQUATORIAL BREAKS

Total: 155.

Retina flat after:

(*a*) Primary basic operation: first attempt, 95; second attempt after (i) first operation, 33; (ii) other procedures, 14.

(*b*) Augmented operation: first attempt, 11; second attempt after (i) first basic operation, 1; (ii) other procedures, 1.

Successes: 145 (94%); failures: 10.

FAILURES

Total: 10.

Nine of these started with little hope of success from the outset and all ended with a shrunken retina. The tenth, a balloon detachment with a solitary horseshoe tear, developed a violent vitreal inflammation 3 days after surgery. Although this subsided on treatment with high systemic doses of steroids and antibiotics, the vitreous cleared only enough to reveal a rigid, partially detached retina.

Of the others 4 might have reasonably been rejected for surgery anyway on the grounds of fibrosis. In another eye a giant horseshoe tear could be just seen through a vitreous haemorrhage. Another, also with a presenting vitreous haemorrhage, had already had argon laser photocoagulation to curb hypertensive new-vessel formation. In 2 cases no healthy sclera could be found after sponges were removed from areas of widespread diathermy which had already induced similar destructive effects in the retinae. The last, grossly myopic and staphylomatous, eye required the easy removal of fluid vitreous because of a shallow detachment. This eye

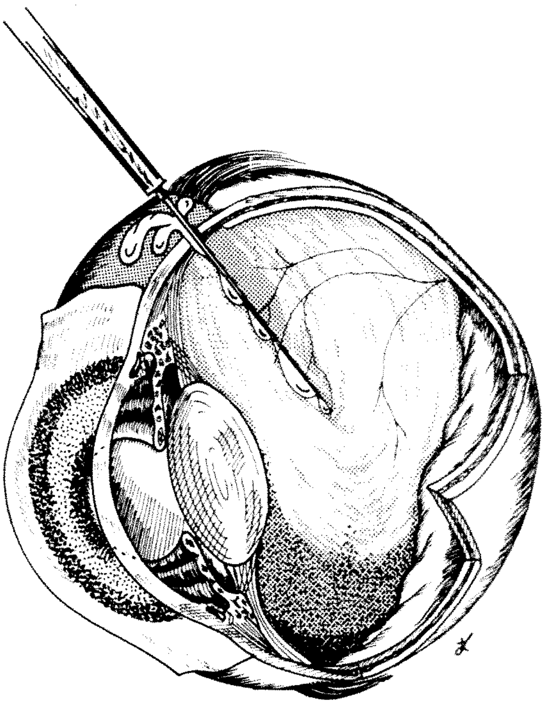

Fig. 2 *Release of fluid from within the vitreous cavity*

never recovered from the shock of surgery and collapsed quickly into phthisis.

APHAKIC DETACHMENTS

Total: 49.

(1) Genuine aphakic tears.

Retina flat after

(*a*) Primary basic operation: first attempt, 15; second attempt after (i) basic operation, 1; (ii) other procedures, 1.

(*b*) Augmented operation: first attempt, 1; second attempt after (i) basic operation; (ii) other procedures, 1.

(2) Other tears with incidental aphakia.

Retina flat after

(*a*) Primary basic operation: first attempt, 11; second attempt after (i) basic operation; (ii) other procedures, 4.

(*b*) Augmented operation: first attempt, 1; second attempt after (i) basic operation, 1; (ii) other procedures.

Successes: 36 (73%); failures: 13.

FAILURES

Total: 13.

Aphakic detachments, even the straightforward ones, have a rather sinister reputation that we have not been able to confirm. All but 1 of our failed cases started out with a poor prognosis but in only 4 of these could gross vitreous loss at cataract extraction be held to blame. Of the remaining 9 there was 1 in which vitreous blood partially obscured the retina. The next very myopic eye became phthisical; 2 more presented with advanced fibrosis.

Three had suffered previous surgery. The first, a young man, lost the lens after a penetrating injury which tore the retina along the equator with a fair degree of vitreal haemorrhage. The primary augmented operation held this retina flat for about 6 months before shrinkage took it beyond the scope of a second surgical attempt. The second, also in the same age group, had had multiple needlings for congenital cataract. A basic operation flattened the retina for a year, after which he relapsed with a fresh tear and suffered a vitreous haemorrhage at the second operation. This was thought to be due to the cryopexy. The third was virtually inoperable following excessive diathermy.

The next eye, on top of its other problems, had a successful corneal graft for interstitial keratitis. Two basic operations failed because a posterior polar tear was not seen at first. This retina flattened partially after a third basic operation during which the cryopexy caused a choroidal haemorrhage; that the graft has survived all these surgical insults may reflect well on the gentleness of the technique.

DIALYSIS

Total: 24.

Spontaneous including one giant tear.

Retina flat after

(*a*) Primary basic operation: first attempt, 18.

(*b*) Augmented operation; first attempt, 1.

Traumatic.

Retina flat after

(*a*) Primary basic operation: first attempt, 2; second attempt, 1.

Successes: 22 (91·6%); failures: 2.

FAILURES

Total: 2.

The first, a moderate myope, with 3 small temporal dialyses, became a surgical catastrophe. A posterior sclerotomy was performed to reduce the intraocular pressure, which had risen out of control for no detectable reason during the operation, and he suffered a vitreous haemorrhage. The second with traumatic retinal detachment and lens subluxation and vitreous haemorrhage, flattened for 6 months before relapsing with preretinal retraction.

MACULAR AND POSTERIOR POLAR HOLES

Total: 13.

Retina flat after

(*a*) Primary basic operation: first attempt, 6. One of these suffered three days postoperatively an acute inflammatory episode in the vitreous which cleared on high doses of steroid and antibiotics. Second attempt after (i) basic operation, 1; (ii) other procedures, 3.

Successes: 10; failures: 3.

Because the retinal elevation in post-polar detachments does not usually advance beyond the equator, subretinal fluid has to be let out beside the more posterior and hence larger choroidal vessels. Should this prove impossible, then, to make way for the air bubble, fluid vitreous can be released in much the same manner as that described for posterior sclerotomy in malignant glaucoma (Scott and Smith, 1961).

FAILURES

Total: 3.

All of these cases were highly myopic. In 2 no explanation could be offered for the failure except poor uptake of cryopexy at the posterior pole. The third eye collapsed into intractable hypotony.

COMPLICATIONS

In our other cases, as well as in those of this series, the most common cause of choroidal or choroido-vitreal haemorrhage is cryopexy, despite careful monitoring of the iceball. However, disabling vitreous haemorrhage occurred in just 2 cases, and flat choroidal haemorrhage gravitated to the macular area in only 3 instances.

Subretinal fluid release produced no significant bleeding but did produce incarceration of the retina on 6 occasions (2 in one patient with bilateral shallow detachments and multiple holes). Because the release site was chosen with this complication in mind, all of these were contained with ease and safety with a little extra cryopexy and the same air bubble or a small scleral infolding buckle.

Choroidal detachment masquerading to the unwary as an actual retinal detachment becomes a complication only when large enough to affect vision. A deliberately eccentric encircling band which blocked half the vortex veins was the culprit in 2 cases which settled when the band was cut. Two further patients complained of a deep ocular discomfort refractory to routine analgesics. The bands were sectioned and the pain settled, but neither these nor any of the others in our series showed any signs of anterior segment ischaemia.

Vitreous inflammation occurred only twice. Of these cases 1 cleared to a great extent, though leaving large trailing vitreous floaters. The second cleared only enough to reveal a traction detachment.

In 1 case a blunt needle allowed air to strip the pars plana. Although in this particular eye the retina was already in the grip of fibrosis, this complication is not irreversible and the air can be removed, just as one would remove subretinal fluid, quite easily, provided its presence in the wrong place is recognised. This mishap can be eliminated by watching for the needle tip before depressing the plunger.

Discussion

It is the current orthodoxy to disfavour the use of intravitreal air for 5 main reasons. It is alleged that the air bubble cannot remain long enough to be useful; that air can bring about permanent changes in the vitreous; that the release of subretinal fluid is too dangerous a practice; that the air bubble can introduce infection; that one cannot visualise the retina through the bubble. This is not our experience.

From the first attempt's success rate alone there can be no reasonable doubt that the air bubble does in fact remain long enough to carry out its task. In none of our cases (even those 8 with diabetes) did the vitreous develop any adverse features that might fairly be ascribed to the harmful effect of air.

Subretinal fluid release need not be dangerous if one does not take liberties with the basic rules. The release site must be scrupulously chosen and marked where the retinal detachment is deep, where the major choroidal vessels can be easily avoided, and where an accidental retinal perforation or incarceration can be contained either by the air bubble or by a small scleral infold. In practice the ideal point lies over the centre of a major equatorial tear should one such be available. If fluid vitreous appears, as it may rarely do, in place of subretinal fluid, the eye is still softened and thus satisfactorily prepared for the intravitreal air injection.

We have found only 1 choroidal-vitreous haemorrhage that could have resulted from this manoeuvre, and, contrary to present belief, we would blame cryopexy as the commonest cause of such haemorrhages, which, if present, occurred prior to the release of subretinal fluid. As for intravitreal infection, only 2 eyes developed a posterior vitreal inflammation, and only 1 of these was left with permanent disability as a result.

If the air is introduced from a dry syringe with a single movement of the plunger, then the bubble will also be single and the retinal view as informative as it was before the injection, provided one views the fundus with the binocular indirect ophthalmoscope, which is unaffected by the gross change in refraction of the eye.

The release of fluid vitreous along a Graefe blade is always a last choice in detachments with multiple holes where just too much subretinal fluid exists to allow tear sealing with a buckle but not enough to allow its safe release. Preoperative slit-lamp examination of the vitreous is essential in all cases, for although deep detachments always present with a very fluid vitreous, so frequently may shallow detachments, which progress slowly as a result of either tiny tears or of a partially solid vitreous cortex. A shallow retinal detachment with a relatively 'healthy' vitreous is most likely to settle with local buckling or encirclement to catch the posterior tear edge, because the retina in these cases is detaching reluctantly.

The inferior rectus stitch has extended the use of air to all inferior tears except those on the 6 o'clock equator, which lie usually too far posterior to be brought uppermost by positioning. Any discomfort due to the stitch is lost in the general discomfort of the operation. The head-down position, although less than pleasant, is maintained rigorously for only 24 hours, and no stitch is ever allowed to remain beyond 48 hours. There has been no evidence of postoperative impairment of extraocular muscle action.

The apparent emphasis on the discussion of failures aims to demonstrate that many of these cases were given the chance of an operation without any confident prospect of success, although in many instances this pessimism proved unfounded. Some

19% of all our patients came to surgery with evidence of preretinal retraction, whether as fixed folds, rolled tear edges, taut opercula, or a rigid vitreous.

We believe that our primary success rate with the need for only one relatively short general anaesthetic must commend this method to more surgeons than those harassed by long operating lists. We contend that this series of 241 cases, accepted with no thought to prognosis, indicates a greater place for the routine use of intravitreal air in retinal detachment surgery.

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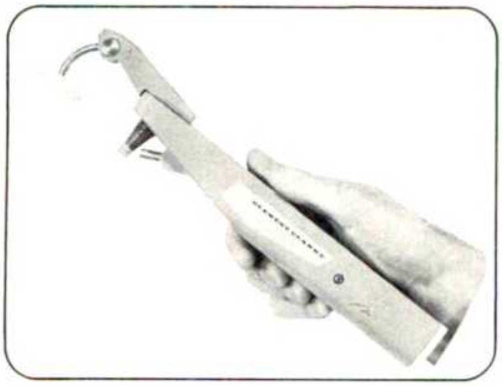

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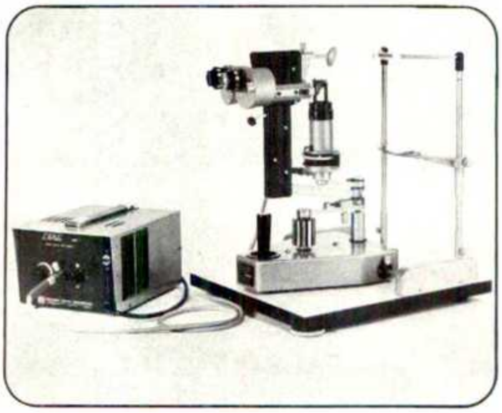

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British Journal of Ophthalmology, 1977, **61**, 593–594

Infection following retinal detachment surgery

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From the Department of Ophthalmology, St. Thomas's Hospital, London

SUMMARY Since the introduction of gentamicin (given both as a soaked sponge and as an injection below Tenon's capsule at the end of surgery) no case of early infection either with or without intraocular signs after operation for retinal detachment has occurred in a series of 206 cases comprising 243 operations. However, late infection many months after operation has appeared in 3 cases (1·5%), though this rate appears to have been favourably influenced by the administration of gentamicin. Local or systemic side effects from the administration of gentamicin have not been seen, and therefore the sub-Tenon injection in the quadrant where the sponge has been placed is strongly advocated in all cases of surgery for retinal detachment when such sponges are used.

Silastic sponge implants used in retinal detachment surgery may become infected. While the infection tends to present with late extraocular granuloma (Lincoff *et al.*, 1970) at a varying length of time after surgery, early infection may occur and be accompanied by intraocular signs (Hitchings *et al.*, 1974). In the latter study the incidence of early infection was 2·4%. In the same series the incidence of extraocular infection was 6% (Chignell, 1974). These early intraocular infections may present considerable difficulty in diagnosis and management (Chignell, 1975). Although extraocular infection may take place many months after surgery has been performed, it is probably the result of organisms introduced at the time of operation. Other factors such as poor suturing technique or the presence of thin sclera will result in scleral sutures cutting out and loss of a snug fit of the sponge to the globe. This may help stimulate granuloma formation or result in local haemorrhage and contribute to the infected buckle syndrome. However, the effect of these factors is hard to assess. It also seems possible for early infection to be caused by retrograde spread of organisms in the immediate postoperative period via the conjunctival wound.

In an attempt to reduce the incidence of both early and late infection we have modified our standard practice by injecting gentamicin below Tenon's capsule at the end of operation. Gentamicin is a bactericidal antibiotic active against a broad spectrum of Gram-positive and Gram-negative pathogens.

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Methods

206 consecutive cases of retinal detachment treated at St. Thomas's Hospital were studied over a 3-year period. The follow-up has varied from 1 to 3 years. A total of 243 retinal detachment operations were performed on these cases, and the operations involved a total of 322 separate pieces of Silastic sponges (149 radial and 173 circumferential sponges). In 42 cases a silicone rubber encircling band was used in addition to a sponge. Before being sutured on to the sclera the sponge (removed from its closed sterile packet at the last possible moment and held in plain non-tooth forceps) was dipped into a bath of gentamicin. At the end of the operation the wound was closed by drawing the conjunctiva and Tenon's layer forward together to be sutured at the limbal incision (King and Schepens, 1974). A sub-Tenon injection of gentamicin 20 mg was given in the quadrant surrounding the sponges.

Results and discussion

No obvious side effects, either local or systemic, followed the administration of the single gentamicin injection at operation. In no cases has there been an early postoperative infection as previously described (Hitchings *et al.*, 1974). Three cases (1·5%) became infected at a varying length of time from the operation. Two of these presented at 6 and 9 months respectively with granuloma formation and mucopurulent discharge. The third case presented with an extruding sponge and recurrent subconjunctival haemorrhage 20 months after surgery. Two infected cases occurred after primary retinal detachment surgery and 1 following a reoperation. In all 3 cases the sponge was removed without redetachment.

It is possible that this infection rate of 1·5% will be higher when the follow-up period becomes even longer, but it seems that the sub-Tenon injection of gentamicin appears to have had a beneficial influence on our own extraocular infection rate, though similar low rates have been reported by other authors using a somewhat different antibiotic regimen—although with a much shorter follow-up (Flindall *et al.*, 1971).

The other point of changed technique in this series was the use of the limbal incision. In addition to saving time and being neat this method appears to provide the implant with a very satisfactory covering, avoiding the necessity of suturing Tenon's layer separately over the sponge. It also ensures that the conjunctival incision does not directly overlie an anterior implant, as was the case with the traditional conjunctival incision. It is not possible to know whether the use of the limbal incision has any beneficial effect on infection, although it may help to reduce the risk of direct spread of organisms from the conjunctiva.

We are indebted to Mrs Margaret Grice for her invaluable secretarial assistance.

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British Journal of Ophthalmology, 1977, **61**, 595–596

Clinical copper metabolism parameters in patients with retinitis pigmentosa and other tapeto-retinal degenerations

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SUMMARY Reports have appeared of abnormal copper metabolism in retinitis pigmentosa, and of a family with vitelliform retinal degeneration in which other members suffered from hepatolenticular degeneration. In the present study 15 patients with retinitis pigmentosa, 4 with various other retinal degenerations, and 1 with a family disposition to retinitis pigmentosa were examined. The copper concentration in serum and the coeruloplasmin concentration in plasma were found to be within normal limits. In 9 of the patients with retinitis pigmentosa the urinary excretion of copper per 24 hours was determined and was found to be normal. The results of the present study lend no support to the hypothesis of abnormal copper metabolism in retinitis pigmentosa.

In view of their findings in patients with retinitis pigmentosa of normal serum copper concentration, reduced plasma coeruloplasmin concentration, and increased urinary excretion of copper Gahlot *et al.* (1976) suggested that retinitis pigmentosa might be caused by a disorder of copper metabolism. We found it worthwhile to perform a similar study, as we were already engaged in metabolic studies of pigmentary retinopathies (Ehlers and Schønheyder, 1977), and because Brink (1974) had reported a family with vitelliform retinal degeneration in which several other members suffered from Wilson's hepatolenticular degeneration, well known as a disorder of copper metabolism.

Material and methods

Twenty patients were included in this study (Table 1). In accordance with the case history and the results of ophthalmoscopy, perimetry, dark adaptation, and electroretinography the patients were classified in 2 groups. The first group (Table 1A) comprised 15 patients with retinitis pigmentosa. The second group (Table 1B) comprised 4 patients with various other retinal degenerations, and 1 patient (No. 18) who had a family disposition to retinitis pigmentosa but showed no evidence of retinal degeneration.

The copper concentration in serum and the coeruloplasmin concentration in plasma was deter-

Table 1 *Material*

Patient no.	*Age in years*	*Sex*	*Diagnosis*
A. 1	10	female	Retinitis pigmentosa
2	12	male	Retinitis pigmentosa
3	14	male	Retinitis pigmentosa
4	15	male	Retinitis pigmentosa
5	17	female	Retinitis pigmentosa
6	17	male	Retinitis pigmentosa
7	22	male	Retinitis pigmentosa
8	27	male	Retinitis pigmentosa
9	37	female	Retinitis pigmentosa
10	51	male	Retinitis pigmentosa
11	52	male	Retinitis pigmentosa
12	57	male	Retinitis pigmentosa
13	57	female	Retinitis pigmentosa
14	61	female	Retinitis pigmentosa
15	62	male	Retinitis pigmentosa
B. 16	14	female	Tapetoretinal degeneration, uncertain type
17	15	male	Stargardt degeneration
18	20	female	Myopia
19	35	female	Flecked retina syndrome
20	50	female	Fundus albipunctatus

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Table 2 *Results*

Patient no.	*Copper concentration in serum (µg/100 ml)*	*Coeruloplasmin concentration in plasma (g/l)*	*Copper urinary excretion (µg/24 h)*
A. 1	100	0·29	—
2	134	0·41	25
3	106	0·30	43
4	126	0·44	—
5	96	0·28	—
6	130	0·35	51
7	*	0·24	47
8	109	0·32	—
9	116	0·32	—
10	110	0·31	68
11	108	0·37	38
12	131	0·34	47
13	128	0·35	13
14	158	0·57	60
15	132	0·41	—
B. 16	122	0·40	—
17	100	0·27	—
18	101	0·31	—
19	125	0·32	—
20	106	0·32	—
Normal ranges (±2 SD)	Male 74 to 146 Female 83 to 159	0·18 to 0·42	9 to 80

*Sample lost in preparation

mined in all the patients by the methods described below. The urinary excretion of copper per 24 hours was determined in 9 of the patients with retinitis pigmentosa.

Copper concentration in serum was determined photometrically by the method of Jensen *et al.* (1964). By double determinations performed at intervals of one week the values could be reproduced with a standard deviation of 3·4 µg/100 ml, corresponding to about 3%. Urinary excretion of copper was determined by atomic absorption. The standard deviation was 9 µg/1. Coeruloplasmin concentration in plasma was determined by radial immunodiffusion by Manzini's method with a standard deviation of about 2·5%.

Results

The findings are shown in Table 2. The concentration of copper was found to be within normal limits in all the patients examined, the average value being 117·8 (SEM 3·65) µg/100 ml. For coeruloplasmin all values except 2 were within the normal range. Patients 4 and 14 had raised concentrations. The average value was 0·346 (SEM 0·0164) g/l. The urinary excretion of copper per 24 hours was found to be within normal limits in all the 9 cases examined, the mean being 43·6 (SEM 5·60) µg/24 hours. It will be seen from the bottom two rows of Table 2 that even an age variation in the normal ranges of about 10–12%, as given by some authors, will not alter the findings of normal parameters.

Discussion

The disorders of copper metabolism reported by Gahlot *et al.* (1976) in patients with retinitis pigmentosa, namely, reduced coeruloplasmin concentration and increased urinary copper excretion, were not found in the present study. Therefore the hypothesis that retinitis pigmentosa might be caused by an inborn error of copper metabolism is not supported.

Of course it is not possible from a limited study like the present to draw definite conclusions; moreover, the diagnosis of retinitis pigmentosa applies to conditions differing with regard to heredity, age of onset, severity, rate of progression, and coincidence with other diseases. Such differences were also evident among the cases classified as retinitis pigmentosa in the present series. It should also be realised that blood levels and urinary excretion are probably not a very sensitive way of investigating copper metabolism. Therefore the observations available so far do not exclude the possibility that some cases of pigmentary retinopathy, or perhaps certain stages in the degeneration, may be related to copper toxicity or to a disorder of copper metabolism.

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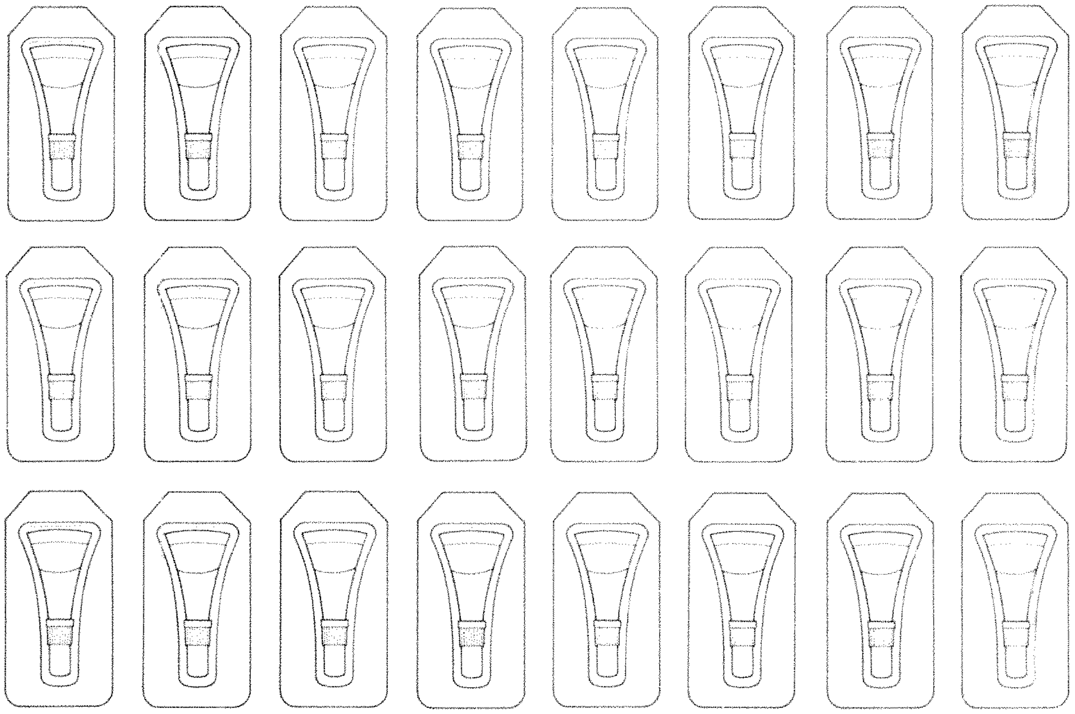

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British Journal of Ophthalmology, 1977, **61**, 597–600

The association of retinitis pigmentosa with preretinal macular gliosis

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SUMMARY A retrospective study of the histopathological features of retinitis pigmentosa was undertaken. A consistent finding in 10 out of 10 eyes from 6 patients with retinitis pigmentosa was the presence of a preretinal membrane. The frequency of this finding has not been noted previously. Preretinal gliosis may well be responsible for the production of the abnormal glinting fundus reflex seen at the posterior pole in retinitis pigmentosa.

The presence of a clinically visible glinting reflex on the retina of patients with advanced retinitis pigmentosa similar to those appearing in patients with idiopathic preretinal gliosis led us to undertake a retrospective histopathological study of eyes with late retinitis pigmentosa. An effort was made to determine whether or not a preretinal membrane was present.

Preretinal gliosis has been reported in a number of different conditions (Wise, 1975). A study of 10 eyes obtained at necropsy from 6 patients with advanced retinitis pigmentosa revealed preretinal gliosis (fibrosis) in all of them. There have been reports of the occasional finding of such a membrane by others, but this has not been previously established as a regular feature of this disease.

Methods

Ten post-mortem eyes from 6 patients with retinitis pigmentosa were selected for study. The age, sex, pertinent medical findings, and cause of death are summarised in Table 1. The more commonly described histopathological features of retinitis pigmentosa were present: pigment cell hyperplasia and migration to the inner retina, degeneration and loss of rods and cones and the thinning of the outer retina, hyalinisation of the arteriolar and venular walls with migration of pigment, intraretinal gliosis, loss of ganglion cell, and bipolar cell loss.

Results

Light-microscopic sections consistently revealed a preretinal membrane on the internal limiting lamina of all patients with late retinitis pigmentosa (Figs. 1 to 3). The membranes were invariably composed of cells with flattened ovoid nuclei and elongated cytoplasmic processes. The membranes were usually 1 cell layer thick, though some areas displayed multiple layers of cells. Wet tissue was not available for study. However, 1 celloidin block was processed for electron-microscopic study. Photomicrographs showed a cellular membrane on the internal limiting lamina which was characterised by filamentary structures and was devoid of melanin granules (Fig. 4).

Table 1 *The age, sex, family history, ocular history, and cause of death of 6 patients with late retinitis pigmentosa*

Age	*Sex*	*Family history/ocular history*	*Cause of death*
54	F	Father, brother, and sister: Retinitis pigmentosa	Carcinoma of breast
47	M	Cataracts	Carcinoma of rectum, tuberculosis of lung
62	M	Poor vision since age 8 years old	Carcinoma of lung
65	M	—	Carcinoma of tongue, chronic alcoholism
40	M	—	Glioblastoma multiforme
47	M	Mother and 4 sibs had retinitis pigmentosa; s/p cataract extraction os; drusen of optic nerve	Carcinoma of colon

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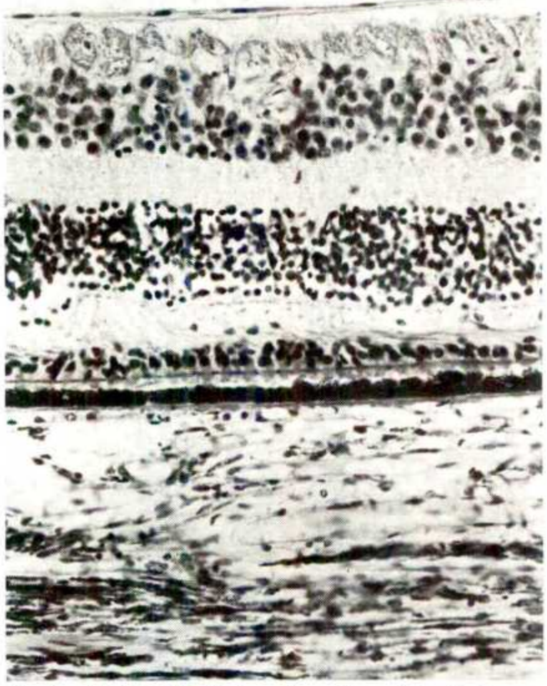

Fig. 1 *129520 OD. Retina of a patient with retinitis pigmentosa shows pigment cell migration and a thin, delicate membrane overlying the internal limiting membrane (H and E.* × 38)

Discussion

There have been sporadic reports of membrane structures on the internal limiting membrane (lamina) in eyes with retinitis pigmentosa (Gonin, 1902, 1903; Verhoeff, 1931; Cogan, 1950; Wolter, 1957; and Eichholtz, 1974).

Verhoeff (1931) described a case of retinitis pigmentosa with tuberculosis of the iris in which he found a neuroglial membrane on the inner surface of the retina. This membrane was 3 or 4 cells thick, and nowhere was it seen communicating with the neuroglia within the retina. Verhoeff also noted a delicate neuroglial membrane over the surface of the disc. Cogan (1950), in an extensive histologic study of 5 cases of retinitis pigmentosa (2 post mortem, 2 enculeated for glaucoma, 1 enucleated for anterior uveitis), observed that the inner layers of the retina occasionally showed a glial membrane extending into the vitreous. Wolter (1957), using the special glial staining method of del Rio Hortega, described 1 case of retinitis pigmentosa in a 75-year-old man who had died in dementia. The patient had been followed up clinically for many years before his death. Wolter concluded that the cause of the waxy pallor of the disc observed clinically was due to a combination of a new formed layer of astrocytes on the inner surface of the papilla, of nerve fibre degeneration, and of the scar formation of glia and connective tissue within the optic nerve

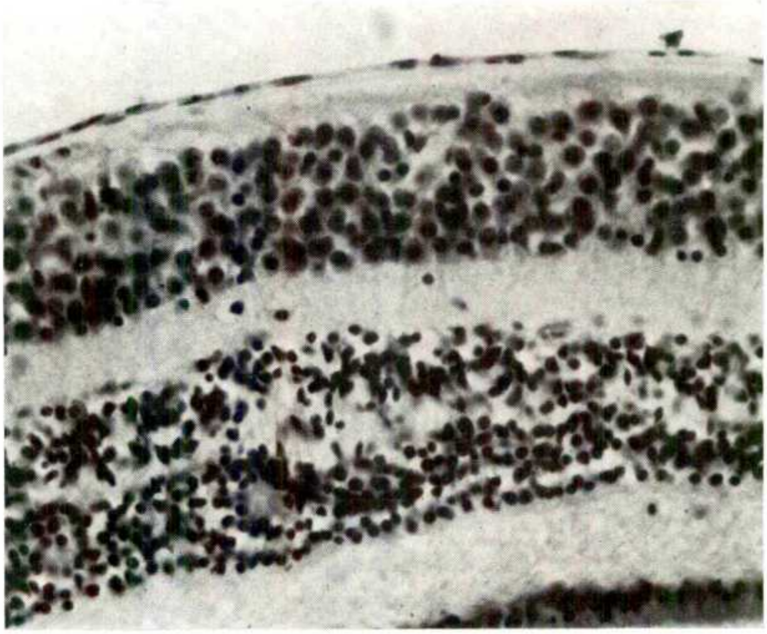

Fig. 2 *129520 OD. Another section of same eye as Fig. 1 showing preretinal membrane (H and E.* × 54)

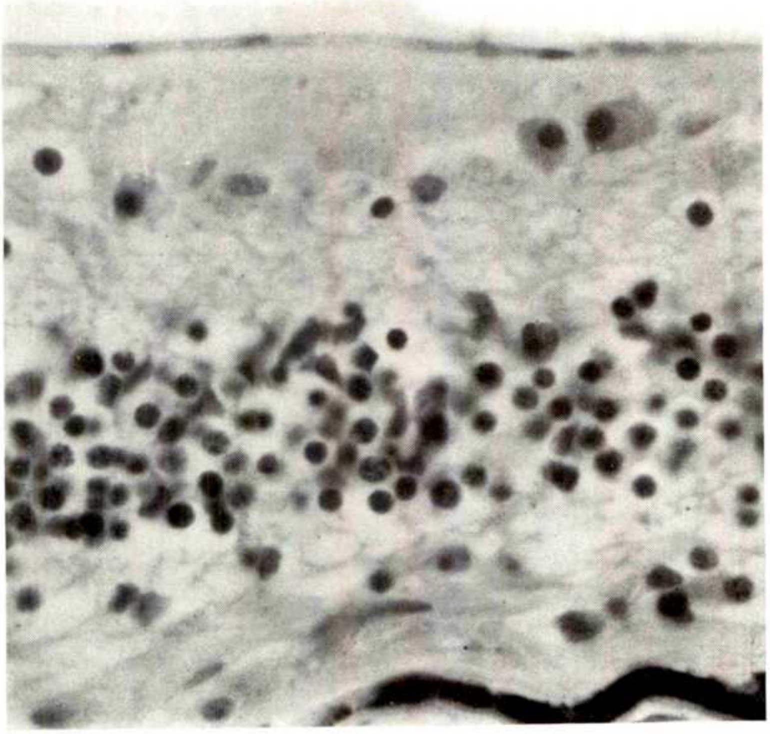

Fig. 3 *18874002. Section of retina showing thin continuous preretinal membrane (H and E. ×137)*

head. Wolter also noted that on the inside of the internal limiting membrane of the retina a new layer of peculiar flat cells with long intertwined processes had developed.

Wise (1975) had classified preretinal membranes according to aetiology (see Table 2).

Roth and Foos (1971) described surface wrinkling retinopathy (macular pucker) in a study of 1000 post-mortem eyes. An epiretinal membrane was present in 3·5% of the specimens described and consisted of 1 or more layers of flattened cells, which usually bridged across the crests of the wrinkles.

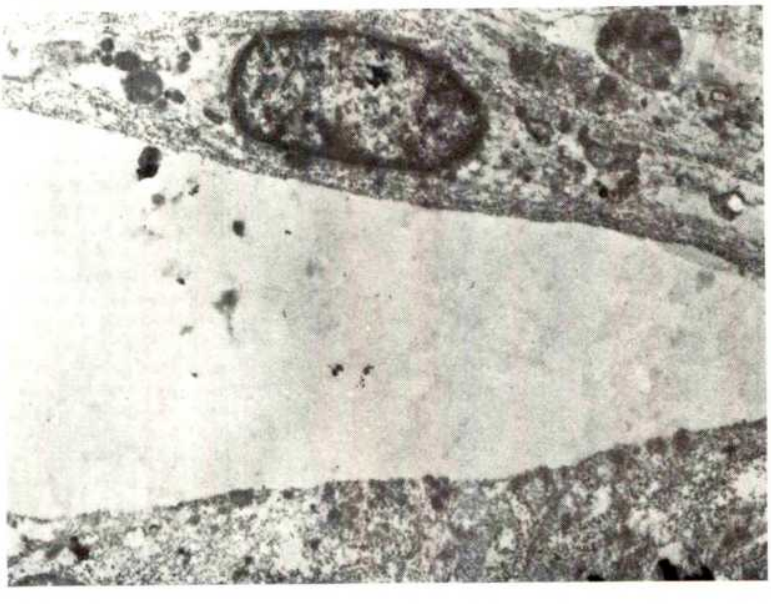

Fig. 4 *Electron-micrograph of preretinal membrane shows prominent nucleus, rough surfaced endoplasmic reticula, numerous fine cytoplasmic microfilaments, and collagen strands.* ×10 900

Table 2 *Classification of preretinal membranes, adapted from Wise (1975)*

1. Idiopathic preretinal macular gliosis
2. Occurring after vascular occlusions
3. Occurring after photocoagulation
4. Congenital
5. Macular pucker after retinal detachment surgery
6. Associated with previous trauma
7. Secondary to inflammation
8. Proliferative reaction after vein obstruction
9. Occurring after cataract extraction

Roth and Foos (1971) concluded that these cells were retinal in origin and arose from focal defects in the inner limiting lamina.

Eichholtz (1974) discussed 2 cases of retinitis pigmentosa, the second of which had had photocoagulation for cystoid macular oedema and then was subsequently found to have a malignant melanoma. Histopathological study showed a preretinal membrane. The author commented that the preretinal membrane may have been associated with the photocoagulation.

Bellhorn *et al.* (1975) described 2 cases of idiopathic preretinal macular gliosis in which a clinically glinting retinal reflex had preceded the development of retinal folds and retinal traction lines. Histopathological study in both cases showed a break in the inner limiting lamina through which glial cells had migrated and had proliferated on the retinal surface. There were no vitreoretinal adhesions. The ultrastructural similarities of these lesions to the preretinal glial membranes seen in other disease entities suggested to the authors the possibility of a common aetiology.

Laqua and Machemer (1975) and Machemer and Laqua (1975) experimentally produced retinal detachments in owl monkeys and noted massive preretinal traction. Cells of retinal origin formed a preretinal membrane and were heavily interdigitated by long cytoplasmic processes. Zonulae occludentes were present, and the cytoplasm often contained bundles of filaments arranged in a parallel fashion. Pigment granules were occasionally seen. It was observed with DNA studies that these cells were astrocytes and that they had grown out of the retina through focal interruptions in the inner limiting lamina and had proliferated.

Kenyon *et al.* (1975), in describing the preretinal membrane seen in pars planitis, observed elongated fibrocytic-appearing cells with thin processes interposed among collagenous aggregates. Rough-surfaced endoplasmic reticula were present, and the authors concluded that these cells resembled fibrous astrocytes.

Clarkson *et al.* (1977) have recently reviewed 2000 eye pathology cases (388 surgical, 1612 post mortem) to determine the prevalence of preretinal membranes. The prevalence of preretinal membranes in surgical cases was 21·5%, while in post-mortem eyes it was 1·7%. A total of 168 cases of previously diagnosed preretinal membranes was also reviewed. Retinitis pigmentosa was not among those cases presented.

We conclude that the glinting retinal reflex of the fundus often described in retinitis pigmentosa is caused by preretinal glial membranes. Ten out of 10 eyes with late retinitis pigmentosa in patients who had never had eye surgery or photocoagulation and who had died of unrelated causes had a preretinal membrane. Electron-microscopic study showed that this membrane was composed of fibrous astrocytes. It is possible that the preretinal membrane which is so consistently present in our cases of late retinitis pigmentosa shares a common aetiology with the preretinal membranes classified by Wise (1975).

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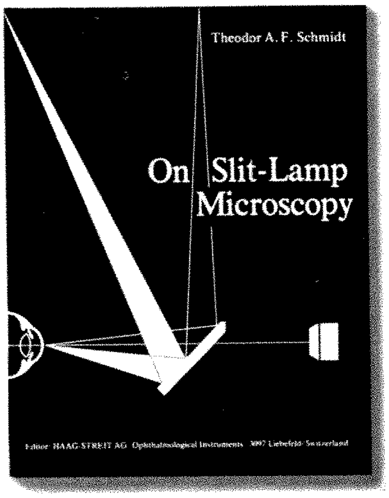
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A microbiological study of neonatal conjunctivae and conjunctivitis

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SUMMARY To investigate the importance of chlamydiae, ureaplasmas, *Mycoplasma hominis*, and anaerobic bacteria in the pathogenesis of neonatal conjunctivitis in the Harrow population conjunctival specimens from 104 infants with conjunctivitis and 104 similar healthy neonates were examined. The incidence of neonatal conjunctivitis was 8·2%, and no case of neomycin-resistant disease occurred during the study. *Staphylococcus aureus*, viridans *Streptococci*, and *Escherichia coli* were the only micro-organisms isolated significantly more frequently from affected than from control eyes, which suggests that these bacteria may be a cause of the conjunctivitis. All cultures for chlamydiae, *M. hominis*, *Neisseria gonorrhoeae*, and anaerobic bacteria were negative. The mother's race, social status, illness, and obstetric events were found to have no effect on the incidence, time of onset of conjunctivitis, or micro-organisms isolated. The clinical characteristics of conjunctivitis were also not related to the micro-organisms isolated. No potential pathogens were isolated from 63·5% of the eyes showing conjunctivitis. The results suggest that some of these cases may be caused by chemical irritation, and the possibility of an infectious aetiology is also discussed.

Neonatal conjunctivitis is a common disease affecting between 2·6% (Watson and Gairdner, 1968) and 5 to 8% (Hurley, 1966) of infants born in England. The inflammation usually resolves spontaneously within a few days and so investigation of the aetiological agent rarely extends beyond routine bacterial culture. This may occasionally reveal *Neisseria gonorrhoeae* infection, which needs urgent treatment to prevent progression of the disease. However, *Chlamydia trachomatis* infections should also be considered. Although these may resolve spontaneously, if untreated they may occasionally result in corneal scarring, which may lead to pannus formation (Freedman *et al.*, 1966; Thygeson, 1971).

An infective agent causing neonatal conjunctivitis is most likely to be inoculated during vaginal delivery of the infant. Pathogens of the disease should therefore be sought among components of the vaginal flora in pregnancy (de Louvois *et al.*, 1975) and among aetiological agents of vaginitis or cervicitis. *C. trachomatis* has been isolated from the cervices of apparently asymptomatic women (Oriel *et al.*, 1974; Burns *et al.*, 1975), but some cases of cervicitis may be caused by this organism (Chiang *et al.*, 1968; Hobson *et al.*, 1976). The evidence for this, however, is less conclusive than it is in the case of non-specific urethritis in men (Dunlop *et al.*, 1965; Schachter *et al.*, 1975; Bowie *et al.*, 1976). There is also evidence to suggest that some strains of *Ureaplasma urealyticum* (ureaplasmas) may cause urethritis (Prentice *et al.*, 1976; Bowie *et al.*, 1976; Taylor-Robinson *et al.*, 1977), and it is possible that ureaplasmas could also be a cause of neonatal conjunctivitis. Jones and Tobin (1968) found *Mycoplasma hominis* in 3·5% of eyes of neonates with conjunctivitis, but infants carrying ureaplasmas or *M. hominis* in the nose, throat, umbilical or genital regions have not had an increased incidence of conjunctivitis (Klein *et al.*, 1969; Foy *et al.*, 1970). There has, however, been no report of the incidence of ureaplasmas on healthy or diseased neonatal conjunctivae, nor has the incidence of chlamydial neonatal conjunctivitis been recorded by use of the McCoy cell technique of isolation.

Over a period of 8 months an attempt was made in a maternity unit to isolate chlamydiae, ureaplasmas, *M. hominis*, and bacteria, including anaerobic species, from the eyes of all neonates with conjunc-

Address for reprints: Dr D. Taylor-Robinson, Division of Communicable Diseases, MRC Clinical Research Centre, Watford Road, Harrow, Middx tivitis and from healthy control infants in order to study the role of these micro-organisms in the disease.

Materials and methods

PATIENTS

Consecutive cases of untreated neonatal conjunctivitis occurring between February and September 1975 in the maternity unit at Northwick Park Hospital were examined. Swabs were taken from those infants who developed purulent conjunctival exudate, and control samples were taken from unaffected neonates on the same ward, matched for age, mode of delivery, and when possible for systemic antibiotic treatment of mother or baby. Permission to take specimens was always given by the mother, to whom information about the study was freely available. The project was approved by the Northwick Park Hospital Ethical Committee.

STUDY DESIGN AND COLLECTION OF SPECIMENS

Samples were taken from both eyes of 104 infants with conjunctivitis and from either the left or right eye of 104 controls, the side sampled corresponding to that involved in the affected baby. To avoid cross-contamination swabs were taken from infants without disease before handling any babies with conjunctivitis. Swabs were not taken while the babies were crying.

The amounts of conjunctival exudate, inflammation of the eyelids, and periorbital oedema were recorded. The conjunctiva was exposed by gentle traction on the eyelid and the following specimens were taken:

(*a*) For bacterial culture, a small (1 μl) disposable plastic bacteriological loop (NUNC) or a fine platinum wire loop was swept over the conjunctiva and immediately streaked out over a chocolate and a blood agar plate. Care was taken to avoid contamination from the skin and eyelashes. A second, similar loop was used to inoculate a 'GC selective agar medium' plate (Oxoid), which was placed in a candle jar. In addition, in 63 out of 104 cases, this loop was first used to inoculate a prereduced blood agar plate, which was immediately sealed in a McIntosh and Fieldes jar containing a new 'Gas-Pak' (Becton, Dickinson, and Co).

(*b*) For mycoplasmal culture a calcium alginate swab was rolled over a portion of conjunctiva and then agitated in 1·5 ml of mycoplasma liquid medium.

(*c*) For chlamydial culture a cotton-wool-tipped ear, nose, and throat swab was drawn firmly over the greatest possible area of conjunctiva and then energetically agitated in 0·8 ml of sucrose-phosphate transport medium (Darougar *et al*., 1970) containing 10% fetal calf serum. This was plunged into liquid nitrogen within 5 minutes.

(*d*) To examine for trichomonads conjunctival exudate was taken with a loop from 32 patients, and a wet preparation was made with saline on a microscope slide. The edges of the coverslip were sealed with nail varnish. Because samples for culture were given priority, smears for trichomonads were made either with exudate already outside the conjunctival sac or after all other specimens had been taken.

The conjunctivitis was treated with local neomycin by the paediatricians if they thought it necessary, and, if not, the affected eyes were swabbed with sterile saline. Neomycin was chosen because it does not affect the growth of chlamydiae. Neomycin-resistant conjunctivitis could then be identified, diagnosed, and, if chlamydial, thoroughly treated with tetracycline ointment.

The infants who had conjunctivitis were observed daily as long as they were in hospital. The district midwives, who visit 76% of babies born in the hospital for up to 2 weeks after delivery, were asked to seek and report cases of conjunctivitis throughout the period of the study. During that time the total number of neonates who developed conjunctivitis in hospital or at home was recorded.

Information about the mothers and infants in the study was collected. This included details of age, race, marital status, occupation, past history of infections and medication, complications of this and any previous pregnancy, the mode of delivery, the condition of the infant, puerperal infections and treatment, and also whether breast or bottled milk was given.

LABORATORY PROCEDURES

The chocolate/blood agar plates were incubated in an atmosphere of 5% CO_2 and, like all the bacterial cultures, at 37°C. The chocolate and aerobic blood agar plates were observed at 24 and 48 hours after inoculation. Thirty of the 63 anaerobic agar plates were incubated for 2 days and the remainder for 3 days before the jars were opened. The procedures necessary to identify any bacterial growth were performed by the staff of the Microbiology Department of Northwick Park Hospital. The gonococcal selective agar plates were incubated in candle jars, examined at 24 and 48 hours, and any colonies were tested with fresh oxidase reagent.

The methods of isolating *Chlamydia trachomatis, Ureaplasma urealyticum*, and *Mycoplasma hominis* were as previously described (Prentice *et al*., 1976).

The wet smears for trichomonads were examined under dark ground illumination within two hours of preparation.

STATISTICAL ANALYSIS

The probability of obtaining a positive bacterial isolation was estimated, with standard errors, for each organism and for each of the following four categories when one eye was chosen at random: (*a*) bilateral conjunctivitis, (*b*) affected eye in unilateral conjunctivitis, (*c*) unaffected eye in unilateral conjunctivitis, and (*d*) no conjunctivitis—controls.

Fisher's exact probability test was applied with one degree of freedom in comparing the isolation of micro-organisms from conjunctivitis cases which occurred within 24 hrs of delivery and those which occurred after the first day of life (Table 1).

Results were considered significant if $P \leqslant 0{\cdot}05$.

Results

INCIDENCE OF CONJUNCTIVITIS

Satisfactory specimens were obtained from 104 affected neonates, though 128 cases of conjunctivitis occurred in hospital during the study period. An additional 35 new cases beginning at home were reported by district midwives. Since only 76% of infants were discharged from hospital into the area visited by the midwives, the expected number of cases of conjunctivitis occurring in infants after leaving hospital is 47. The 128 cases in hospital and 47 estimated at home results in a total of 175 babies affected out of 2142 infants delivered in that period. The incidence of neonatal conjunctivitis in the Harrow area is therefore estimated to be 8·2%.

MICRO-ORGANISMS ISOLATED

The conjunctivitis was present in one eye in 59 neonates and in both eyes in 45 neonates. Specimens were therefore taken from 149 eyes showing conjunctivitis, 59 normal-looking opposite eyes of affected babies, and 104 eyes of healthy control infants. The micro-organisms isolated from these three groups are listed in order of frequency in Table 2.

Table 2 *Micro-organisms isolated*

Micro-organism	*Eyes with conjunctivitis (149)*	*Normal-looking opposite eyes of patients with conjunctivitis (59)*	*Control eyes (104)*
Staph. epidermidis	31 (21%)	13 (22%)	33 (32%)
Staph. epidermidis (alone)	(15)	(10)	(28)
Viridans *Streptococcus*	25 (16%)	4 (6·8%)	3 (2·9%)
Staph. aureus	12 (8%)	5 (8·5%)	3 (2·9%)
E. coli	8 (5·4%)	—	1 (1%)
U. urealyticum	5 (3·4%)	—	2 (1·9%)
Pseudomonas sp.	2	—	—
Klebsiella sp.	2	—	—
Proteus sp.	—	—	1
Neisseria sp.	1	—	—
Corynebacterium ulcerans	1	—	—
Diphtheroids	2	1	—
Str. pneumoniae	1	—	—
Non-haemolytic *Strep.* sp.	1	1	—
Micrococcus sp.	1	—	—
Aerobic spore-former	—	—	1
No isolate	80 (53·5%)	39 (66%)	65 (62·5%)
Any micro-organism isolated	69 (46%)	20 (34%)	39 (37·5%)
Any micro-organism isolated, excluding *Staph. epidermidis*	54 (36%)	10 (17%)	11 (10·5%)

Staphylococcus epidermidis was the organism isolated most frequently from all groups, but the isolation rate in the conjunctivitis group (21%) was not significantly different ($P>0{\cdot}05$) from that in the control groups (32% and 22%).

Viridans *streptococcus* was isolated from 25 (16%) eyes showing conjunctivitis, 4 (6·8%) opposite eyes, and 3 (2·9%) control conjunctivae. The difference in isolation rates for the affected and control eyes was significant whether the disease was unilateral ($P<0{\cdot}01$) or bilateral ($P<0{\cdot}05$). In addition the difference between the isolation rates for the affected eyes and the opposite eyes was significant ($P<0{\cdot}05$), but was not significant for the opposite eyes when compared with the controls ($P>0{\cdot}05$).

Staphylococcus aureus was isolated from 12 eyes showing conjunctivitis, 5 opposite eyes and 3 control eyes. The isolation rate in the conjunctivitis group was significantly different from that in the

Table 1 *Relationship between the infants' age at the onset of disease and the presence of micro-organisms*

Age at onset of conjunctivitis	*No. of patients*	*No. of eyes with conjunctivitis*	*No. of eyes with no micro-organisms isolated*	*No. of eyes with any micro-organisms isolated**
0–12 hours	4	8	8	0
13–23 hours	5	9	9	0
1–2 days	43	64	38	26
3–6 days	44	56	20	36
> 6 days	8	12	5	7

*Significant difference in isolations before and after 24 h ($P<0{\cdot}006$).

control group ($P<0{\cdot}05$) when the disease was unilateral but not when bilateral. When the isolation rate of the affected group was compared with that for unaffected opposite eyes, there was no significant difference ($P>0{\cdot}05$).

Escherichia coli was isolated from 8 eyes showing conjunctivitis and from 1 control eye. This difference in isolation rate was significant ($P<0{\cdot}05$). *E. coli* was not isolated from any of the unaffected opposite eyes.

No other micro-organism was isolated frequently enough to permit statistical analysis. No bacteria grew under anaerobic conditions if they did not appear in the aerobic media. *Neisseria gonorrhoeae*, *Mycoplasma hominis*, and *Chlamydia trachomatis* were not isolated from any patient, nor was *Trichomonas vaginalis* seen in any specimen examined.

More than one species of micro-organism were isolated on 21 occasions from eyes with conjunctivitis, on 4 occasions from unaffected opposite eyes, and on 5 occasions from control eyes. In the majority of cases *Staph. epidermidis* was the other organism in the combination, being isolated with another micro-organism on 15 occasions from diseased eyes, on 3 occasions from unaffected opposite eyes, and on 5 occasions from control eyes.

Since *Staph. epidermidis* is usually a skin commensal, the number of times this bacterium was isolated alone was subtracted from the results (Table 2). The frequency of isolation of micro-organisms from eyes with conjunctivitis was then found to be greater than from opposite eyes of the affected infants ($P<0{\cdot}01$) or from control eyes ($P<0{\cdot}01$). These differences in the frequency of isolation could be due to differences between subjects. However, this is not likely because there was no significant difference between the frequency of isolation of micro-organisms from opposite eyes of affected infants and from control eyes.

ONSET, SIGNS, AND DURATION OF CONJUNCTIVITIS

(1) *Neonatal age at onset.* Half of the cases of conjunctivitis began within the first 48 hours of life. No micro-organisms were isolated from any of the 9 neonates who developed conjunctival exudate within 24 hours of delivery (Table 1). In this respect these 9 infants are significantly different ($P<0{\cdot}006$) from those whose disease started after the first day of life. The fact that 8 of the 9 infants had bilateral conjunctivitis was also significant ($P<0{\cdot}02$). The signs and duration of conjunctivitis, however, were similar irrespective of time of onset. Furthermore, following the first day after birth, the types and incidence of micro-organisms isolated were also unrelated to the time of onset of the disease.

(2) *Signs of conjunctivitis.* The amounts of inflammation of the eyelids, periorbital oedema, and conjunctival exudate were subjectively graded into 4 categories according to severity. None of these categories was particularly associated with the presence of a micro-organism, nor was it related to the time of onset of disease.

Seven healthy control infants subsequently developed conjunctivitis between 2 and 7 days after the swabs were taken. The disease occurred in the eye previously swabbed in 4 babies and in the opposite eye in the other 3. When these babies were swabbed again, the bacteria isolated did not correspond to those isolated from the eyes of the original affected babies for which the former infants were controls.

(3) *Duration and response to treatment.* The observed duration of conjunctivitis is shown in Table 3. Two days after delivery 36% of all babies born in the hospital were discharged home, and therefore only 64 (61·5%) of the patients were watched until their signs disappeared. This occurred within 6 days of onset in about 80% of the cases, whether or not treatment was given. In one neonate of 27 weeks' gestation signs persisted for more than 2 weeks. *Staph. aureus* was isolated, and the conjunctivitis was treated with neomycin for a week. Two days later the exudate recurred and *Staph. aureus* was again isolated. After a further 6 days of neomycin therapy the signs finally resolved. No case of neomycin-resistant conjunctivitis was seen during this study.

EFFECT OF MATERNAL FACTORS ON CONJUNCTIVITIS

(1) *Race.* 79·8% of the mothers of babies with conjunctivitis and 77·9% of the control group were Caucasian. Of the remainder, 12·5% were of Asian origin in both groups, and 7·7% of the conjunctivitis group and 9·6% of the control group comprised mainly West Indian or African negroes. The incidence and types of micro-organisms isolated

Table 3 *Duration of disease and effect of treatment*

Duration (days)	*Total no. of patients*	*No. of untreated patients*		*No. treated with neomycin*	
< 2	7	7		0	
3–4	24	9	80%*	15	76%*
5–6	19	12		7	
7–8	8	6		2	
9–10	2	0		2	
11–12	3	1		2	
14+	1	0		1	
Unknown	40	30		10	
Total	104	65		39	

*Excluding unknown group

from the non-Caucasian babies were similar to those isolated from the Caucasian babies.

(2) *Marital and social status.* The mothers of 8 (7·7%) infants with conjunctivitis and the same number of mothers of infants in the control group were unmarried. The age of these infants at the onset of the disease and the incidence and types of micro-organisms isolated were no different from those of the babies of married mothers.

The proportion of parents in social classes I and II with affected infants was 32·5%, which is similar to that of the healthy babies, 38·5%.

(3) *Maternal disease and antibiotic treatment.* A past history of urinary tract infection was given by the mothers of 20 affected and 19 healthy neonates. The types and incidence of micro-organisms in the conjunctival specimens from these infants were no different from the rest of the population studied. *E. coli* was isolated from only 1 baby with conjunctivitis whose mother had had urinary tract infection. The results were also similar whether or not the mothers had been pyrexial since their delivery or had taken antibiotics during the pregnancy or in the puerperium.

(4) *Amniocentesis and mode of delivery.* Although amniocentesis may provide an opportunity for the introduction of infection, the onset of conjunctivitis was no earlier in the 19 infants whose mothers had had this procedure performed during the pregnancy. Furthermore, the micro-organisms isolated from this group were similar to those isolated from the rest of the infants examined.

The composition of the conjunctival flora in infants who developed conjunctivitis after a difficult delivery, the use of forceps, or a delivery delayed more than 24 hours after rupture of the fetal membranes was similar to that seen in babies delivered with ease. The micro-organisms isolated from the conjunctivae of the 12 affected infants born by caesarian section were also no different from those in the eyes of the infants born by vaginal delivery.

OTHER FACTORS AFFECTING CONJUNCTIVITIS

Neither the gestational age of the infants, nor the presence of coexisting disease bore any relation to the micro-organisms isolated. The weights of 26% of the infant population studied were below the 50th centile for gestational age, and ureaplasmas were isolated from only 1 infant in this low-birthweight group.

Breast milk was fed to 63% of the patients and to 75% of the healthy infants examined. *E. coli* was isolated from the eyes of 1 healthy breast-fed baby and 6 infants with conjunctivitis. Four of the latter were bottle-fed, and information on feeding was not available for the remaining 2 infants.

Discussion

Despite our ability to isolate chlamydiae from up to 47% of men suffering from non-specific urethritis, in the present study chlamydiae or gonococci were not isolated from conjunctival specimens of 104 neonates with conjunctivitis. This is in contrast to the results of some other workers. Thus, Sowa *et al.* (1968) cultured chlamydiae in yolk sacs from 4% of affected neonates in the Gambia, where trachoma is endemic. Hansman (1969) diagnosed chlamydial infection in 3%, Watson and Gairdner (1968) in 9%, and Armstrong *et al.* (1976) in 28·5% of neonatal conjunctivitis cases. Chlamydiae were detected in the latter three studies despite use of the relatively insensitive technique of cytological examination of conjunctival scrapings. The McCoy cell culture technique, however, has been shown to be at least twice as sensitive as cytological examination (Darougar *et al.*, 1970) and also more sensitive than yolk sac isolation (Gordon *et al.*, 1969). In Liverpool, Rees and Hobson (1974) used McCoy cells and isolated chlamydiae from 32% of a selected group of neonates whose conjunctivitis did not resolve after neomycin treatment. In addition they found gonococci in 20% of this group of patients.

An authoritative opinion (*British Medical Journal*, 1974) suggests that gonococcal conjunctivitis occurs at a rate of one case per year in a large maternity unit and that the incidence of chlamydial infection is of a similar order. Dunlop (1975), however, claims that chlamydiae cause neonatal conjunctivitis at least five times more often than gonococci in the East End of London. At Northwick Park Hospital only 1 case of gonococcal neonatal conjunctivitis has been diagnosed in three years, and chlamydiae have been isolated from 6 neonates with persistent conjunctivitis at the hospital, although this is not a routine diagnostic procedure. This infrequent isolation of chlamydiae is in keeping with the failure to isolate them in the present study. In addition chlamydiae are insensitive to neomycin, but no case of neomycin-resistant conjunctivitis occurred. It seems reasonable to conlude, therefore, that chlamydial infection is a rare cause of neonatal conjunctivitis in the Harrow population.

Ureaplasmas were isolated from only 4 babies with conjunctivitis and from 2 control babies, the results suggesting no association between the presence of ureaplasmas on the conjunctivae and signs of conjunctivitis. There is, however, evidence of varying pathogenicity among bovine strains of ureaplasmas (Gourlay *et al.*, 1972) and it has been suggested that some strains of human ureaplasmas cause disease in the male urogenital tract while others are harmless commensals (Prentice *et al.*, 1976). In view of this and the few ureaplasma-positive cases seen in this study, the results do not eliminate ureaplasmas as aetiological agents of a small proportion of cases of neonatal conjunctivitis.

Since the micro-organisms mentioned above do not seem to be a main cause of conjunctivitis in the Harrow population, and perhaps other populations too, there arises the question of which other micro-organisms may be implicated in the disease. The isolation of *Staph. aureus*, viridans *Streptococcus*, and *E. coli* was statistically related to the presence of conjunctivitis, and in these cases we presume that the bacteria are pathogenic. *Staph. epidermidis* was not considered to be involved in the disease, since it was isolated at least as frequently from unaffected eyes. Furthermore no anaerobic bacteria were isolated from 63 patients or equal numbers of control infants, so there is no evidence that vaginal anaerobic bacteria can survive on the neonates' conjunctivae. Similarly, *Trichomonas vaginalis* was not seen in specimens from 32 affected infants, a finding which is in keeping with the negative observations of Thygeson (1971). Although trichomonads were observed by Novotný (1973) in 2 cases of neonatal conjunctivitis, it is not known whether they caused the disease.

No micro-organism was isolated from 53·5% of eyes with conjunctivitis, and only *Staph. epidermidis* was isolated from a further 10%. The fact that cultures of specimens taken from infants with signs of conjunctivitis on the first day of life were uniformly negative suggests the possibility of chemical irritation as a cause in these cases. In others chemical irritation may also be a cause, but unidentified microbial infection, either bacterial or viral, cannot be ruled out. It is unlikely that herpes simplex virus is a cause, particularly in the absence of generalised disease (Nahmias and Hagler, 1972), since it is rarely found in the cervix in pregnancy. In view of this, and because there was insufficient conjunctival exudate to increase the number of specimens taken, culture for this virus was not attempted in this study. Nevertheless, it is possible that another virus producing a brief self-limiting disease is involved in some of the cases. Although it seems less likely that an undetected neomycin-sensitive organism is involved, the presence of such an agent may be confirmed or dismissed by a controlled study of the effect of neomycin therapy on the signs of disease.

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Late ocular manifestations in neonatal herpes simplex infection

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SUMMARY Five patients who had had neonatal herpes simplex virus infection were re-examined at ages that varied from 6 to 9 years. In all of them the diagnosis had been supported by virus isolation and antibody titration, and herpes virus type 2, the genital strain, had been the causative agent. Only 1 of the patients was mentally retarded. Three of the patients had manifest squint, and only 1 patient had normal visual acuity in both eyes. The fundus changes varied from atrophy of the retinal pigment epithelium in 3 patients to atrophy of the optic disc in 2 eyes and extreme tortuosity of the retinal arterioles and veins in 1 patient. One patient developed bilateral retinitis with exudation into the vitreous at the age of 5 years. Fluorescein angiography of this patient showed peripheral vascular closure and preretinal neovascularisation, with leakage in both eyes. This may have been due to chronic retinal vasculitis; haemorrhagic infarction may have induced the damage to retinal tissues. Laser photocoagulation resulted in slight improvement of the visual acuity, clearing of the vitreous, and decrease of the fluorescein leakage.

Ocular manifestations of herpes simplex virus (HSV) infection in the newborn include conjunctivitis, keratitis, cataract, and chorioretinitis (Hagler *et al.*, 1969; Nahmias and Hagler, 1972). In a series of 297 cases of neonatal HSV infection 17% had ocular involvement. Microphthalmia, keratitis, or conjunctivitis were noted within the first day of life, while some infants had cataract, chorioretinitis, or optic atrophy later. Corneal scars or recurrent keratitis were also important sequelae (Nahmias *et al.*, 1976). Chorioretinitis may have a variety of appearances, though histopathological studies have shown that the process is limited to the retina and the pigment epithelium, with minimal secondary infiltration of the choroid and the vitreous (Cogan *et al.*, 1964; Young *et al.*, 1965; Cibis, 1975).

Published reports suggest that retinal changes in infants with mild herpes infection without evidence of central nervous system involvement are rare, and little information is available on possible late ocular manifestations of neonatal HSV infection. We therefore now describe the findings of an ophthalmic follow-up study on children surviving after neonatal HSV infection.

Patients and methods

The study is of 5 children who had suffered a neonatal HSV infection. The birth weight and the duration of the pregnancy of each patient are listed in Table 1. The diagnosis had been made by virus isolation and antibody titration. Herpes virus type 2 was the causative agent in all cases where the type had been determined. Because the early symptoms and the clinical and virological studies of these patients have earlier been reported in detail (Pettay *et al.*, 1972) these aspects will be reviewed only briefly in this paper.

At the time of the follow-up study the patients were 6 to 9 years of age. In 4 cases the general physical and mental development had been unremarkable; one patient was mentally retarded. All patients received a thorough ophthalmic examination, including fundus photography and in one case fluorescein angiography as well.

Table 1 *Birth particulars of the 5 cases*

Case	*Sex*	*Age at follow-up (years)*	*Birth weight (g)*	*Duration of pregnancy (weeks)*
1	M	6	1600	36
2	F	7	3600	44
3	F	9	2320	33
4	F	7	2440	36
5	M	9	3290	40

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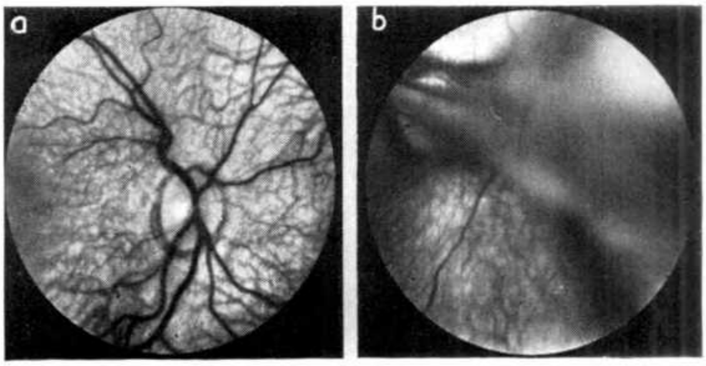


Fig. 1*a, b* Case 3 (a) *Right fundus shows an elliptical optic disc and atrophic retinal pigment epithelium.* (b) *Left disc and macular area are covered by a thick fibrovascular preretinal fold*

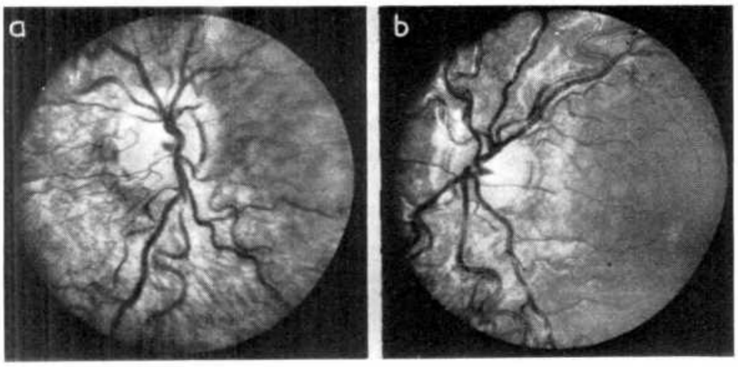


Fig. 2*a, b* Case 1 *Atrophy of the retinal pigment epithelium round the optic discs and extreme tortuosity of the retinal arterioles and veins*

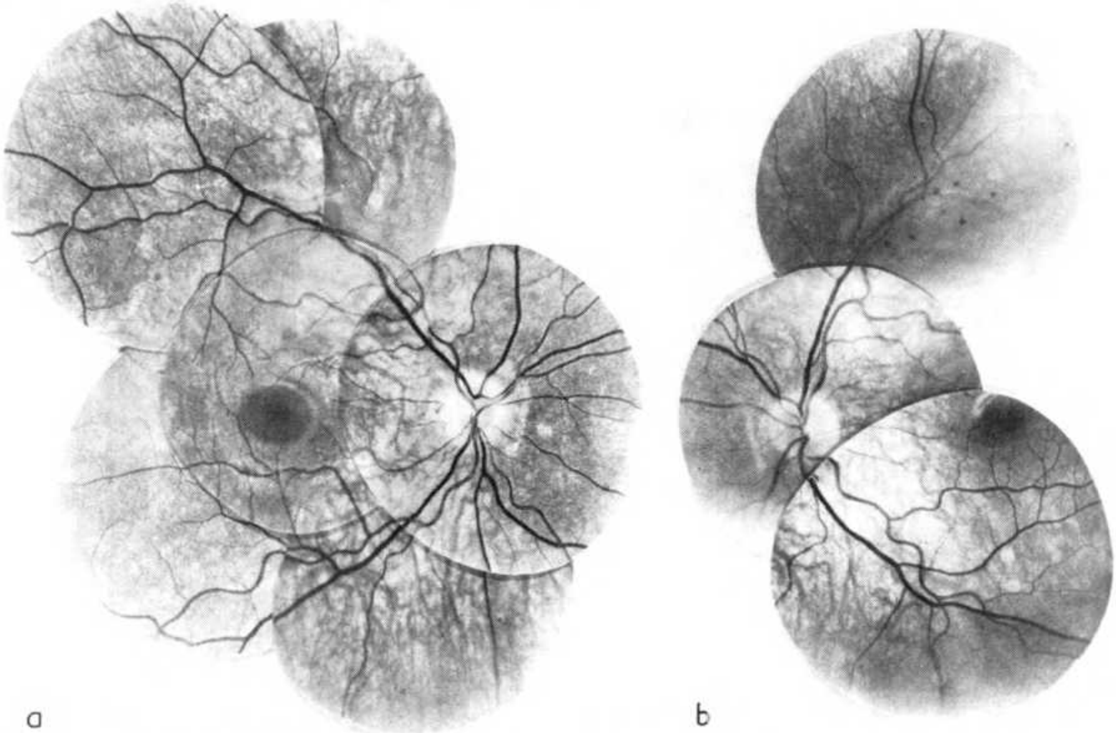
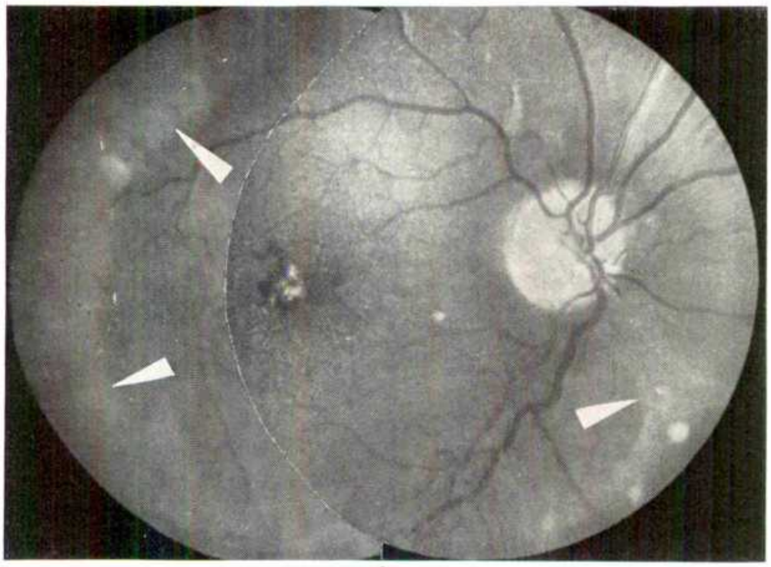


Fig. 3*a, b* Case 5 *Atrophy of the retinal pigment epithelium in the central areas*

Table 2 *Late manifestations of neonatal herpes simplex virus infection*

Case	*Visual acuity*		*Refraction*		*General comments*	*Lens*		*Vitreous*	
	Right eye	*Left eye*	*Right eye*	*Left eye*		*Right eye*	*Left eye*	*Right eye*	*Left eye*
1	0·5	0·5	−1·50	+1·50	Mentally retarded	Clear	Clear	Clear	Clear
2	0·15	1·0	+2·0	+2·25	Right exotropia	Clear	Clear	Clear	Clear
3	c.f.	c.f.	−3·0	+3·0	Left esotropia	Clear	Clear	Clear	Fibrovascular fold
4	0·7	1·0	−2·25	+2·25	Alternating exotropia	Clear	Clear	Inflammatory exudation	Clear
5	1·0	1·0	−1·25	−1·0		Clear	Clear	Clear	Clear



4a

Fig. 4*a, b* Case 4. (a) *Right eye. Fundus photograph showing pale disc, attenuated arteries, and greyish preretinal membrane surrounding the posterior pole* (arrows). *Dilated capillaries and intraretinal white exudates in the centre of the macula.* (b) *Left eye. Comparable picture, changes less pronounced*

Results

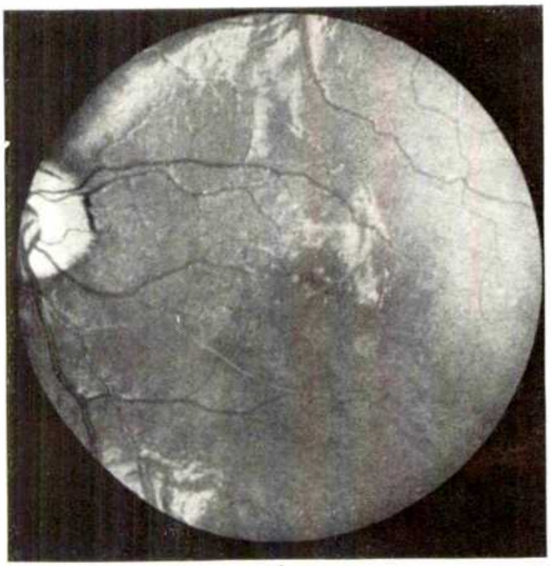
The visual acuities and refractions at the follow-up examination are listed in Table 2. Only 1 patient (case 5) had normal visual acuity in both eyes. The refractions were not remarkable, but 3 of the 5 patients had manifest squint. The ocular tensions were within normal limits. The lenses were clear, but the vitreous contained inflammatory exudation in 1 patient (case 4) and a thick fibrovascular fold in one (case 3, Fig. 1*a, b*).

The optic discs were pale in 2 eyes (cases 2 and 3). The retinal manifestations included atrophy of the retinal pigment epithelium, especially round the optic disc on 3 patients (cases 1, 3, and 5; Figs. 2*a, b*; 1*a*; 3*a, b*) allowing visualisation of the choroidal vascular system and extreme tortuosity of the retinal arterioles and veins (Fig. 2*a, b*). The inflammatory manifestations in case 4 are described in the following case report.

CASE REPORT

Case 4 was a girl with a birth weight of 2440 g, prematurely born at 36 weeks gestation. At birth she had several groups of vesicles on both arms as well as several pale round 5-mm spots, many of them surrounded by a ring of crusts, on the back and on both sides. Her general condition was good, no other signs of infection were observed, and later development was normal. The virus (herpes virus

Optic disc		*Retina*	
Right eye	*Left eye*	*Right eye*	*Left eye*
Normal	Normal	Atrophy of the pigment epithelium around the optic disc, highly tortuous arterioles and veins	As the right eye
Pale, anomalous almost like coloboma	Normal	Normal	Normal
Normal	Pale, atrophic	Atrophy of the retinal pigment epithelium around the optic disc	Fibrovascular fold extending to the vitreous
Normal	Normal	Posterior oedema, attenuated arteries, dilated capillaries and intraretinal white exudates	Glistening retina, attenuated arteries, some faint greyish spots
Normal	Normal	Atrophy of the retinal pigment epithelium around the optic disc	As the right eye



4b

type 2) was isolated from the throat, the CF herpes antibody titre was slightly raised, and an unusually high peripheral eosinophilic count, 8000/mm^3 (8×10^9/l), was recorded. Cytomegalovirus and varicella antibody titres were negative.

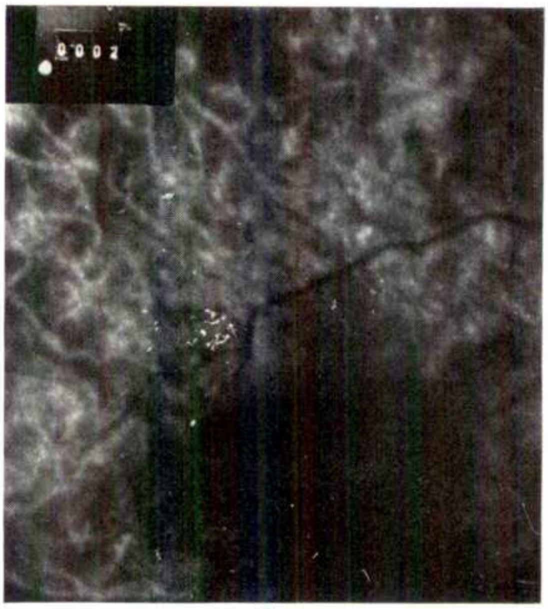
During the post-partum period nothing remarkable was found in the eyes on routine ophthalmoscopy. At the age of 5 years, however, the central visual acuity of the right eye was found to be slightly decreased, and ophthalmoscopy showed some vitreous opacities and mild preretinal and retinal changes in both eyes. During the 2-year follow-up no obvious progression was observed. The findings in each eye were as follows.

Right eye: The central visual acuity (VA) was 0·7. The anterior segment was normal, but some vitreous opacities were seen, particularly in front of the macula. The disc was pale, and the main arteries were narrow, with some sheathing. In the centre of the macula a small white slightly raised intraretinal exudate was found surrounded by dilated capillaries, and another smaller white spot was present temporal to the disc. In the macular area the retina was slightly oedematous, and round the posterior pole the fundus was greyish and glistening, owing to a thin preretinal membrane (Fig. 4*a*). On the nasal side this was already seen by the optic disc. Several small tufts of neovascularisation were found on the margin of the normal-looking retina. The peripheral retina was atrophic without any visible blood vessels, but the choroid looked normal.

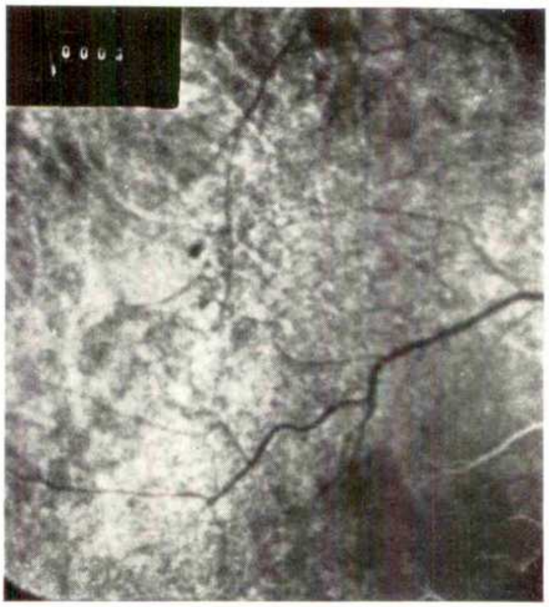
Left eye: The central VA was 1·0, and the media was clear. The optic disc was normal, but the main arteries were narrow and sheathed as in the right eye. Changes in the macula were less pronounced (Fig. 4*b*), but some faint greyish spots and streaks were seen in the centre of the macula. Round the posterior pole the retina was glistening, as in the right eye, and the periphery was atrophic and avascular, but neovascularisation was not seen.

Fluorescein angiography of the right eye temporal to the macula showed filling of the main choroidal vessels (Fig. 5*a*) and of the choriocapillaris (Fig. 5*b*) before filling of the retinal artery, and considerable peripheral non-retinal perfusion (Fig. 5*c*). Immediately temporal to the macula there was dilatation of the retinal capillaries, with progressive leakage of the dye into the retina (Fig. 5*d*). In the mid-periphery there was multifocal hyperfluorescence derived from preretinal new vessels (Fig. 5*e*, *f*).

Fluorescein angiographic study of the left eye (Fig. 6*a*) showed considerable anomaly in the vascular architecture of the macula. There were



5a



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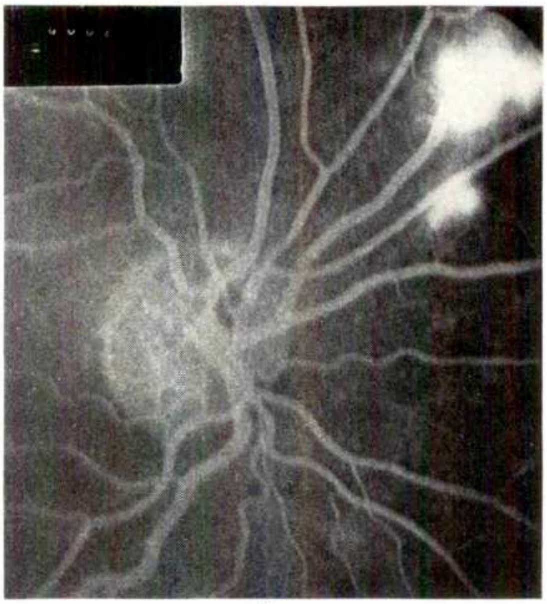
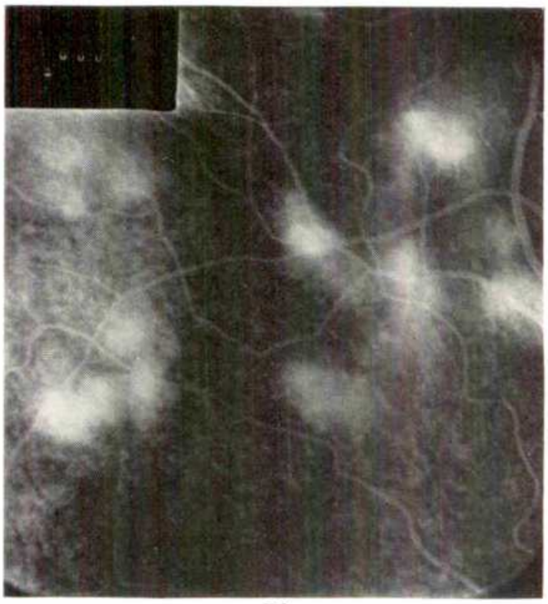


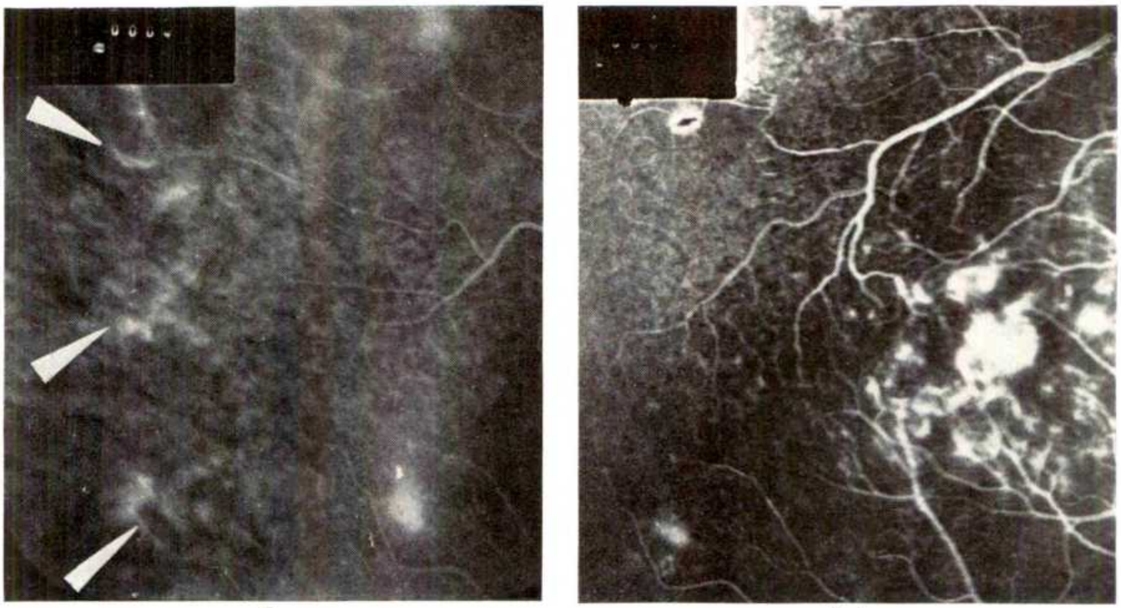
5e



5f

large arterial branches in the close proximity of the fovea and no capillary free zone was present (Fig. 6*b*). Very few capillaries were seen temporal to the fovea and some of them were dilated and leaked fluorescein (Fig. 6*c*). Around the posterior pole normal capillary bed was not perfused (Fig. 6*d*), and several arteriovenous vessel arcades were seen at the margin of the ischaemic area (Fig. 6*c*). A few small leaking areas (Fig. 6*e*)—presumptive preretinal new vessels—were also seen in the left eye in angiography.

Because of preretinal exudation and neovascularisation laser treatment was carried out on the right eye. Preretinal and leaking vessels were treated directly if possible except in the centre of the macula, and simultaneously a sparse grid of



5c

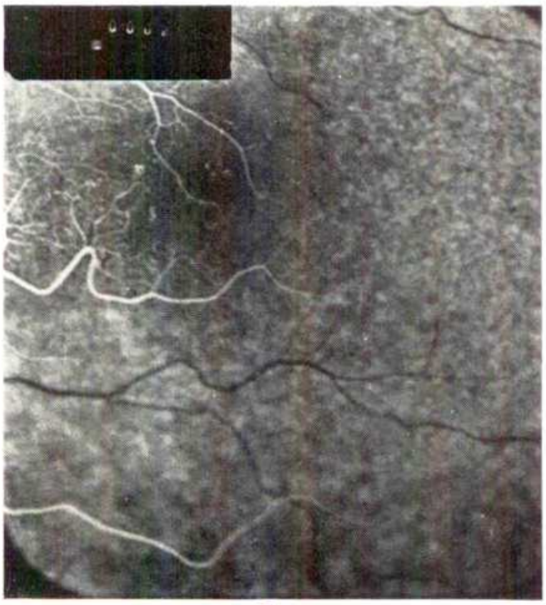
5d

Fig. 5*a–f* Case 4 *Right eye. Choroidal vessels* (a) *as well as diffuse fluorescence of the choriocapillaris* (b) *clearly visible owing to retinal and pigment epithelial atrophy. Delayed and slow filling of retinal arteries as compared with choroidal circulation* (b). *Dilated leaking capillaries on the margin of the non-perfused retina temporal to the macula* (c) *and in the macula* (d) (arrows). (e, f) *Pretreatment fluorescein angiogram, late venous phase. Leakage of fluorescein from preretinal vessels superonasally* (e) *and above the macula* (f)

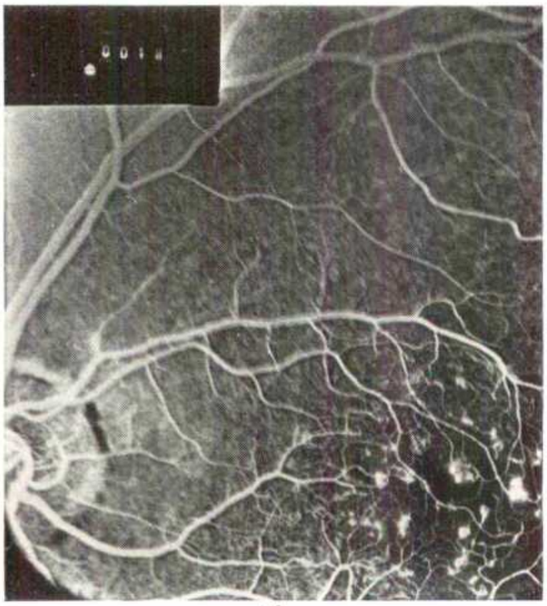
coagulations was applied along the border of the non-perfused retina round the posterior pole. The treatment was carried out in 4 sessions with about one month apart using 1·0 to 0·5-mm spot size; 763 burns altogether were applied. During this period visual acuity improved slightly from 0·7 to 0·8 and vitreous opacities decreased. Fluorescein angiography 2 months after the initial treatment showed considerably less leakage of fluorescein as compared with the pretreatment situation (Figs. 5*e*, *f*; 7*a*, *b*).

Discussion

HSV ocular involvement in the newborn is easily overlooked, particularly if the general manifestations are absent. The differential diagnosis of herpetic



6a



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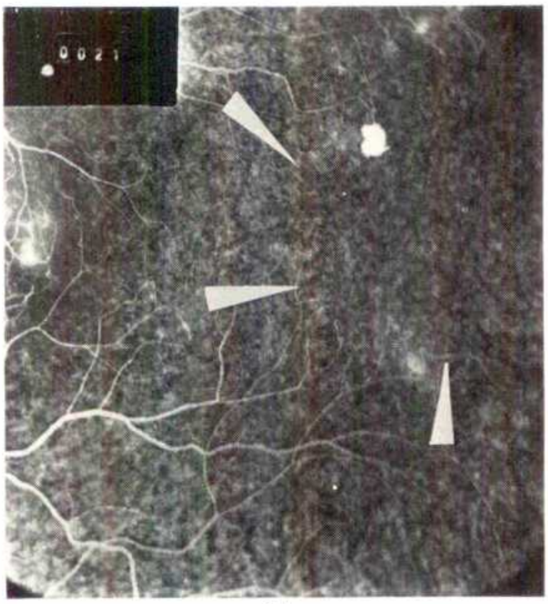

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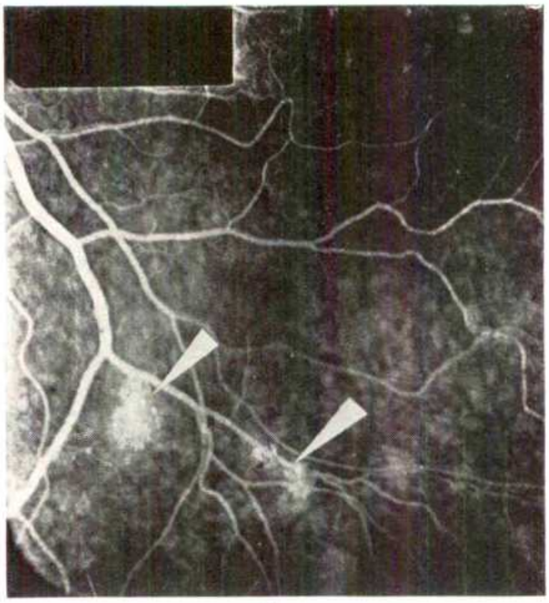
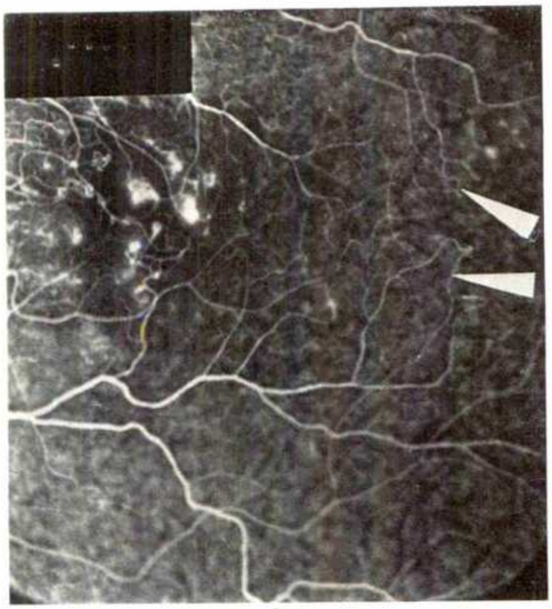


6e

retinitis includes toxoplasmosis, rubella, cytomegalovirus infection, and syphilitic chorioretinitis. In our cases the diagnosis had been confirmed by virus isolation and antibody titration.

Manifest squint in 3 patients may be explained by poor visual acuity in one or both eyes. Case 2 had a deeply amblyopic right eye with no fixation and had been operated on for cosmetic reasons. Atrophy of the retinal pigment epithelium could be due to prematurity, as cases 1 and 3 had birth weights under 2500 g, but similar atrophy was also found in case 5 with birth weight within the normal range. One may conclude that we are dealing with sequelae of neonatal HSV retinitis. These include also the thick fibrovascular retinal fold extending into the vitreous in the left eye of case 3.



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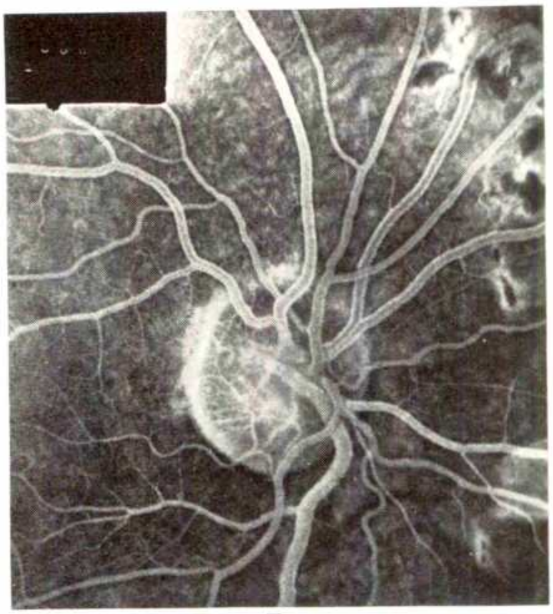
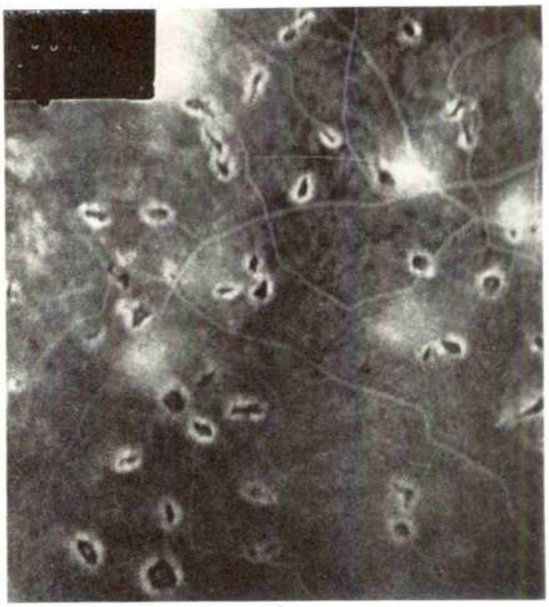


7a

Fig. 6*a–e* Case 4 *Left eye. Good view of choroidal fluorescence even in the macular area* (a). *Delayed and slow filling of retinal arteries as compared with choroidal filling.* (b) *Abnormal vascular architecture in the macula with some dilated and leaking capillaries in the centre.* (c, d) *Several arteriovenous communications* (arrows) *on the margin of the avascular retina temporal to the macula.* (e) *Leaking areas along the course of the inferotemporal veins* (arrows)



7b

Fig. 7*a, b* *Same areas as in Fig. 5*e, f, *2 months after initial laser treatment. Considerably less leakage than before treatment*

The great majority of ocular manifestations in neonatal herpes simplex infections have been described within the first months of life (Hutchison *et al.*, 1975). Ten patients have been described with chorioretinitis detected mostly between 30 and 90 days after birth (Nahmias and Hagler, 1972). In our case 4 the changes were not detected until the age of 5 years.

Fluorescein angiographic studies on herpes simplex retinitis have not been reported before. The late changes described in one of our patients are restricted to the retina, whereas the choroid looked normal. This finding is in agreement with the two histopathological studies available (Cogan *et al.*, 1964; Cibis, 1975). Retinal vascular closure found by fluorescein angiography is suggestive of a chronic retinal vasculitis. Perivascular inflammatory reaction has also been described in other tissues in herpes simplex infection (Reynolds *et al.*, 1975). Haemorrhagic infarction may therefore be the possible cause of tissue injury in herpes retinitis. Both the limitation of the process to the retina and the symmetrical affection of both eyes are presumptive of an immunological rather than a direct viral infection in this particular case, as Cogan *et al.* (1964) and Cibis (1975) have suggested. Neither of these authors identified viral inclusions in the retina. The absence of choroidal involvement has also been reported in congenital cytomegalic inclusion disease, in which the condition was primarily a retinal infection with minimal choroidal involvement in the presence of complete retinal necrosis (Tarkkanen *et al.*, 1972).

Preretinal neovascularisation is a common complication in several eye diseases with retinal vascular closure. As in our case 4, new vessels are usually situated at the margin of the ischaemic area. But in this case the new vessel tufts were smaller than in many other diseases, and several were present. Because of the danger of further proliferative changes laser treatment was carried out on the right eye to destroy both neovascularisation and the hypoxic areas round the posterior pole.

Since the clinical course and appearance of herpetic eye lesions may vary, all patients with neonatal herpes simplex infection should have ophthalmic examinations at regular intervals. The ophthalmologist has a crucial role in the early recognition and management of the ocular effects of congenital HSV infection.

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Book reviews

Clinical Refraction and Visual Science. J. R. LEVENE. 1977. Pp. 346, figs., tables, refs. Butterworth, London (£12·50)

This small book consists of 12 chapters which are in fact historical essays on various topics of clinical refraction and visual science. The first deals with Dr William Porterfield (1696–1771). Others follow on ocular refractive errors, accommodation, bifocals, trifocals, night myopia, astigmatism, and finally the contact lens. Each essay gives evidence of considerable scholarship and first-rate library work, combined with a style that shows the author has an intense and loving interest in the subject. The book will provide a useful source of reference for all scholars interested in the history of clinical optics. If a further edition is called for, I would advise that the title be changed to 'Historical Essays in Clinical Refraction', otherwise this work will not obtain the selective readership it so readily deserves. MONTAGUE RUBEN

Atlas of Diseases of the Anterior Segment of the Eye. Vol. 5. The Crystalline Lens. DAVID D. DONALDSON. Pp. 209, 129 figs., 112 stereo views. Kimpton, London (£44·30)

Although this is an expensive book and as such beyond the reach of many ophthalmic students, it is a splendid book. It is written with a rare clarity, and in most instances its accounts of abnormalities of the lens are comprehensive. Very occasionally descriptions of the lenticular changes lack exact information indicating the positioning of the lens opacities and their colour.

The book begins with the anatomy and embryology of the crystalline lens and then passes on to congenital anamolies before discussing presenile disorders, cataracts in systemic changes, traumatic cataracts, and irradiational and toxic cataracts. Finally, surgical complications are adequately covered. With most disorders a simple and explicit description precedes one or two individual case histories, which are supplementary though tedious to read through. Abundant monochromatic illustrations are present throughout the book and are of excellent quality. I. M. DUGUID

Leukaemia and Lymphoma in the Nervous System. CARL POCHEDLY. 1977. Pp. 229, 12 figs., 11 tables. Charles C Thomas, Springfield, Illinois ($23·50)

This book has a little over 200 pages which are intended to contain an 'in depth view' of clinically relevant aspects of a therapeutic field which is rapidly increasing. It is obviously not intended for ophthalmologists, as its coverage of leukaemic involvement of the eye consists of 3 pages of text, and this despite the fact that 9% of children with acute leukaemia may have eye involvement. The eye photographs would not find a place in any ophthalmologist's collection. Although generally comprehensive, the book's lack of any mention of central nervous system afflictions indirectly associated with leukaemia, such as progressive multifocal encephalopathy and measles encephalitis, is regrettable. Many of the diagrams and most of the cytology photographs seem useful only in their ability to break up the text. The rest of the book is of some value, and the comprehensive and up-to-date references at the end of each chapter together with an excellent name and subject index will be of particular interest to paediatricians. DAVID TAYLOR

Diabetic Retinopathy. A. URRETS-ZAVALIA. 1977. Pp. 125, figs., refs. Masson, Paris (no price given)

This is a very full and thoughtful monograph covering all aspects of diabetic retinopathy written by a worker with some 20 years' experience in this field. The work starts with a general account of the prevalence of diabetic retinopathy and a review of the published figures of its incidence and its importance as a cause of visual disability and blindness. This is followed by 2 chapters dealing with the individual fundus signs, clinical types, and natural course of the disease. The vascular changes and the formation of exudates are clearly described and compared with the corresponding fluorescein angiograms. The classification which results is conventional. The disease is divided into simple and proliferative forms and subdivided into well-recognisable clinical types. This is helpful from the viewpoint of the indication for treatment, but it is stressed that the signs and combinations of signs are diverse and do not necessarily follow any definite sequence, a fact that many authors have overlooked.

The most important sections of the book are those on treatment of the various forms of retinopathy. On the medical side clofibrate and a diet low in animal fat are advocated for maturity onset exudative maculopathy, and calcium dobesilate (Doxium) is reported on with more enthusiasm than is its usual lot. Pituitary ablation 'constitutes a legitimate and effective procedure when performed in young subjects without nephropathy and without serious circulatory disturbances'.

About a third of the whole book is devoted to photocoagulation and there are many excellent photographs showing argon laser and xenon arc techniques in use in many different situations. Most of the methods employed and the dosage used follow orthodox lines, but there are some thought-provoking ideas such as ablating the retroequatorial part of the retina in the treatment of disc new vessels. There is a good section on the indications for vitrectomy and the use of ultrasound in the selection of cases. There is an extensive and well selected bibliography.

This book has come at a time when the American and British controlled trials have indicated the effectiveness of photocoagulation and the need to screen and treat the eyes of the growing diabetic population. It is a first-class exposition of the indications and methods of treatment available, is concisely written, and is well illustrated—a 'must' for any departmental library or an individual working in this difficult subspecialty. J. H. DOBREE

Eye Movements and Psychological Processes. Edited by R. A. MONTY and J. W. SENDERS. 1976. Pp. 550, figs, tables, refs. Laurence Erlbaum Associates, Hillsdale, New Jersey (£27)

This book, based on a symposium held in April 1974, contains sections on most aspects of the psychophysics and physiology of eye movements and their role in the visual system and in perception. It is regrettable that this field has been somewhat overlooked by ophthalmologists because it encompasses a wide range of phenomena that not only are immensely interesting but also form a basis for the diagnosis of organic disease often mistaken as functional. The first chapter, in five sections, describes the physiology of eye movement control as understood in 1974, and there is a chapter on techniques of recording and measuring eye movements. The other five chapters relate eye movements to the maintenance of vision, to visual perception, detection, and scanning, and to reading and higher mental processes. There are inevitably some gaps in the area covered, but the individual chapters, many of which are written by distinguished investigators, are coherent and interesting. Although several other books published in the last few years have covered this subject, this one is particularly well laid out and carefully edited. It will appeal not only to physiologists interested in vision and eye movement but also to a few clinicians continuing to widen their education. D. TAYLOR

Electronystagmography: Technical Aspects and Atlas. By J. U. TOGLIA. 1976. Pp. 160, figs, tables, refs. Charles C Thomas, Springfield, Illinois ($13·50)

Eye movement laboratories, with equipment and staff of varying quality, are being set up not only in major centres but, in some countries, even in small private practices, causing onlookers to speculate on the reasoning behind this expansion. That there is need for a concise text for clinicians and the technicians on the recording of eye movements is not in doubt. Although this book does not completely fulfil the need, it comes some way towards doing so. The author, who undoubtedly has a wide experience of electronystagmography, provides the reader with an extensive bibliography mainly derived from the ENT literature. This bias in his experience is reflected in the frequent use of unfamiliar terms such as 'nystagmus—ex-anopsia' and 'nystagmus—ex-amblyopia'.

After a discussion of historical and technical aspects of electronystagmography the author gives guidelines for the clinical evaluation of nystagmus and the interpretation of eye movement records. There then follows an atlas containing about 40 case records from the 10 000 that he has compiled over the 10 years to 1973. Many of these cases illustrate the clinical usefulness of electronystagmography and others illustrate how the technique contributes to the understanding of the pathophysiology. The records, unfortunately, are often not entirely clear and would have perhaps benefited from a certain amount of editing, though it is rather refreshing to see eye movement records published without being touched up either by computer or by hand. The book may appeal to some ophthalmologists but will more probably find a home in the library of ENT practioners and institutions. D. TAYLOR

Der Augenarzt. Vol. 4. By K. VELHAGEN. 1976. Pp. 674, figs, tables, refs. Georg Thieme, Leipzig (DM134)

This volume of 'The Ophthalmologist' is the fourth of a comprehensive series on ophthalmological subjects. It comprises four sections on uveal disease, sympathetic ophthalmitis, ophthalmology applied to driving and road traffic (Verkehrsophthalmologie), and neurophthalmology. Each section is almost a book in itself, with a different author and extensive references. The chapters on uveal disease and neurophthalmology, with concise texts and clear illustrations, are highly recommended for postgraduates, though one would have preferred to see more fundus photographs rather than drawings in the former. Sympathetic ophthalmitis is now a very uncommon disease, and the chapter on it is largely historical. The discussion on traffic medicine and its ophthalmological significance is long and detailed, and one becomes aware that this subject, which assumes a great importance in European, particularly German, ophthalmology, receives only brief attention in English postgraduate training. T. J. FFYTCHE

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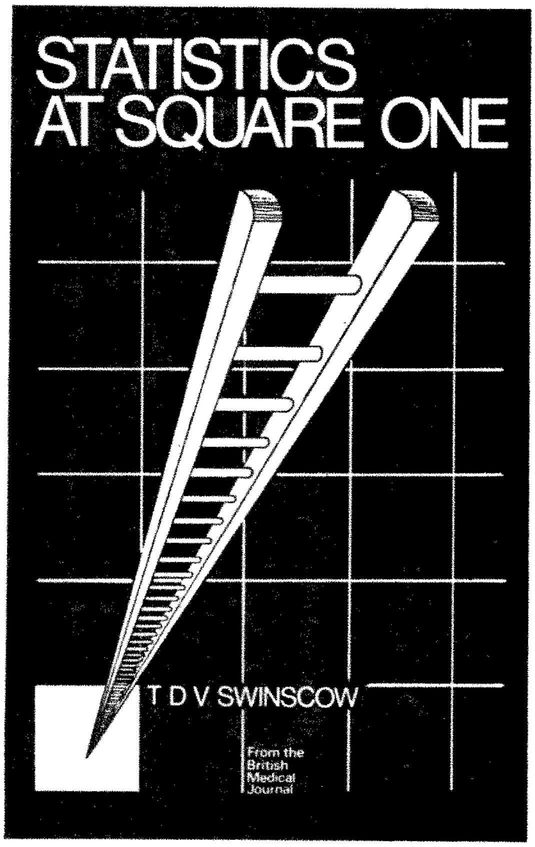

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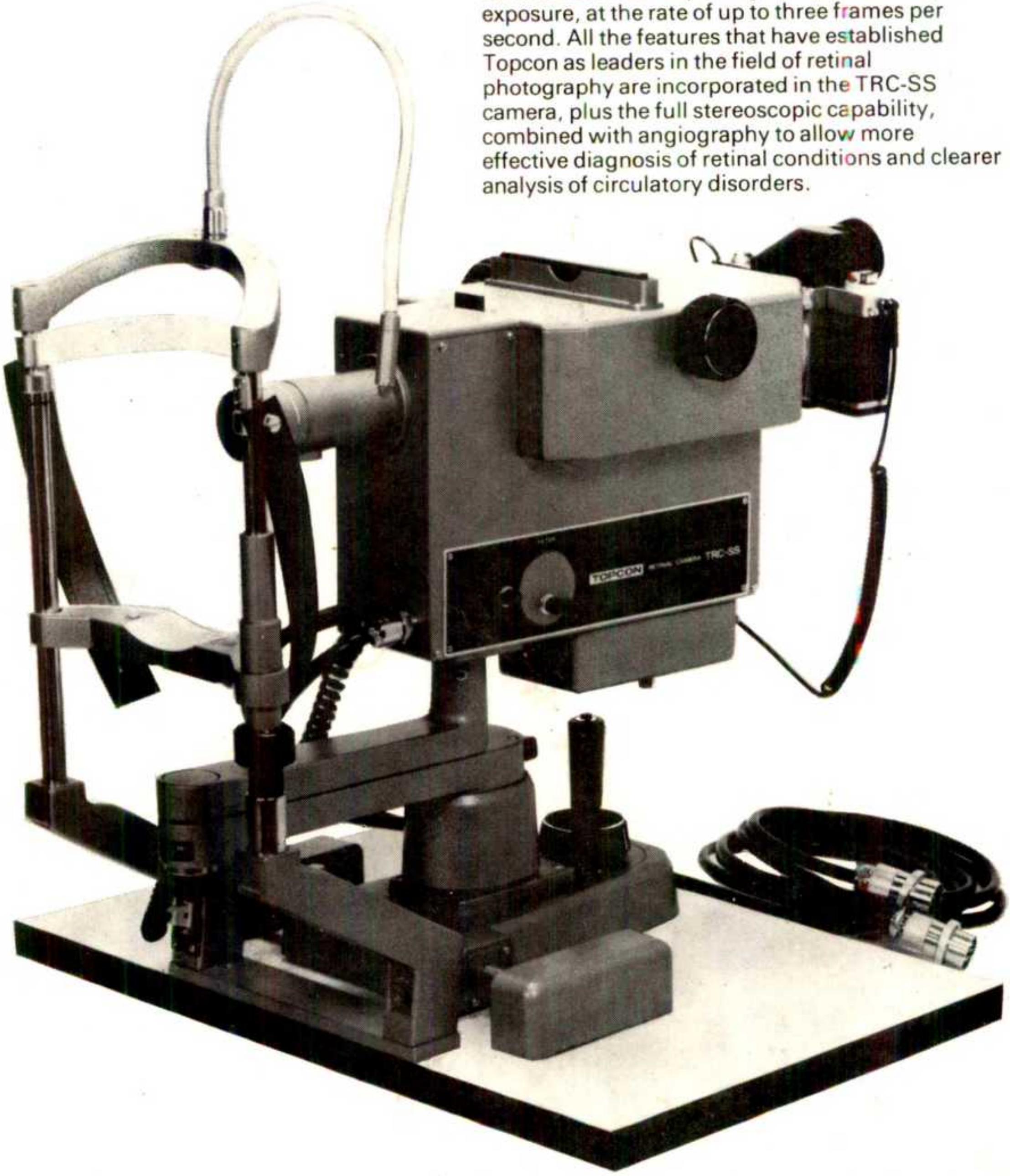

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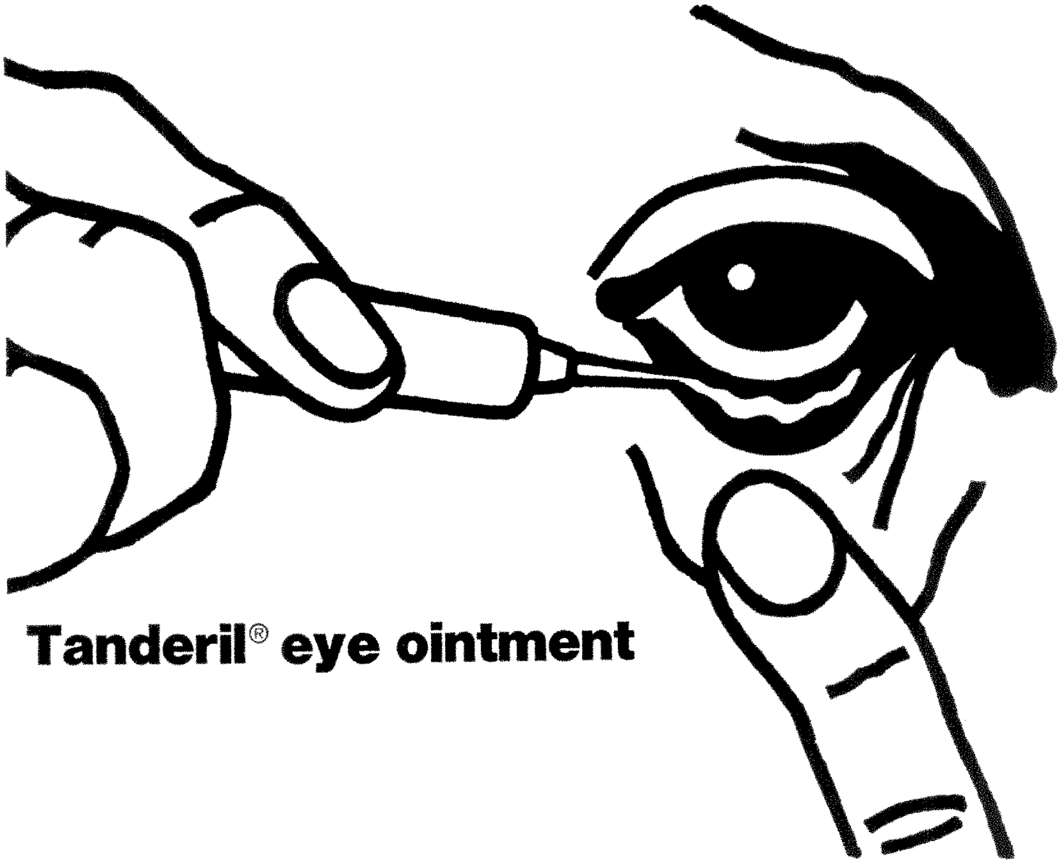

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Tuesday, 31 January—CORNEA. Chairman: Claes Dohlman. Speakers: D. P. Choyce, Richard Forster, C. Stephen Foster, Kenneth Kenyon, Peter Laibson, Deborah Pavan-Langston. **COSMETIC SURGERY**—Chairman: Pierre Guibor. Speakers: Howard Beale, Crowell Beard, Richard Coburn, Frank Gillen, Robert Simons, Dowling Stough.

Wednesday, 1 February—CONTACT LENS UP-DATE. Chairman: Antonio Gasset. Speakers: D. P. Choyce, Dean Clements, Jay Enoch, Stuart Eriksen, Gerald Feldman, John Glotfelty, Paul Honan, William Houde, Kenneth Michaile, John Morgan, O. D. Priddle, Perry Rosenthal, Montague Ruben, John Scabocsik, Harold Stein, Seymour Traeger, Tom Upham, John Williams III.

Thursday, 2 February—RETINA. Chairman: Harvey Lincoff. Speakers: David Abramson, J. Donald M. Gass, Evangelos Gragoudas, Ingrid Kreissig, Fritz Hollwich, Ronald Michels, Marvin Rotman, Howard Schatz, Lorenz Zimmerman.

Friday, 3 February—PAEDIATRIC OPHTHALMOLOGY. Chairman: Donelson Manley. Speakers: Anthony Caputo, Enrique Gutierrez, John Hermann, David Hiles, Philip Knapp, M. L. Kwitko, James Mims, Julian Morales, Zane Pollard.

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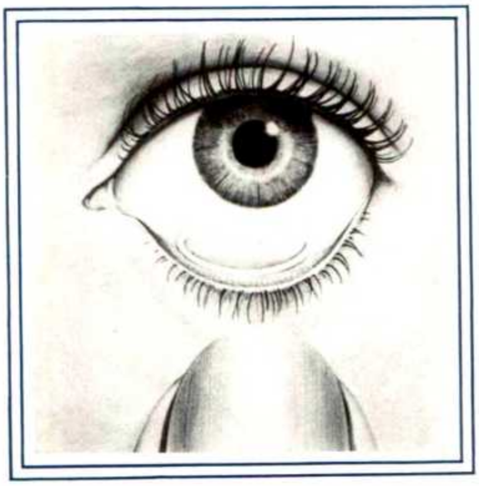

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Edited by Stephen Lock and Heather Windle

A man of stature—in all ways—Henry Miller occupied a large part in many people's lives and his death in 1976 left a large gap. Though a neurologist of world renown he was best known in the North-East, where he spent most of his life, and where, for the last eight years of it, he was Vice-Chancellor of the University of Newcastle upon Tyne. A cross-section of his many friends and colleagues have contributed their reminiscences to **Remembering Henry** *and, as each person saw him from a different angle, those who did not know him will find that the whole man gradually comes to life. Professor John Walton has written the introduction, three of Henry Miller's best-known articles are included (writing was his first interest after neurology), and there is a bibliography of his prolific publications. A fitting tribute,* **Remembering Henry** *may fill some of the gaps for those who have stayed behind. Profits from the book will be given to the Henry Miller Memorial Appeal.*

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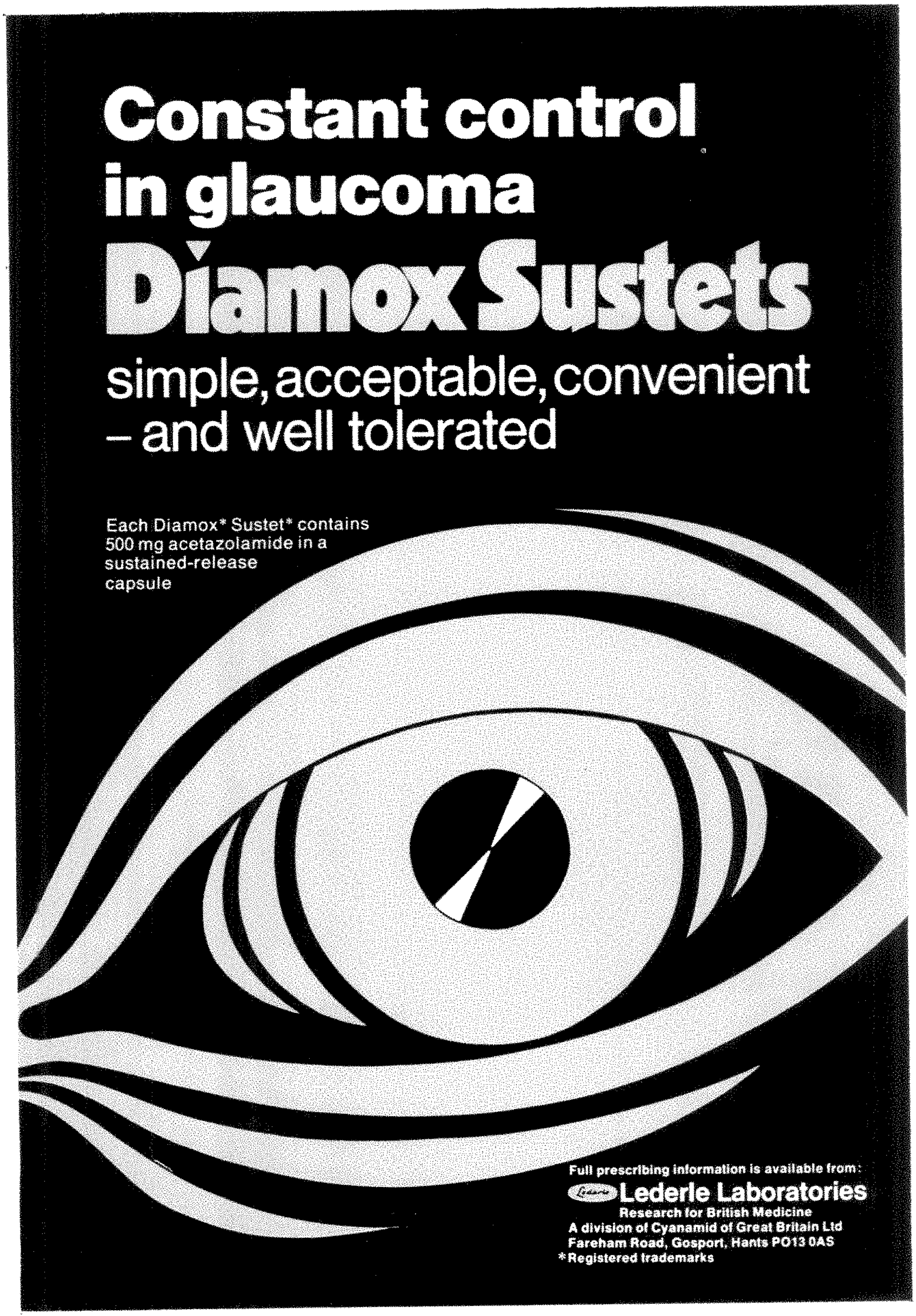

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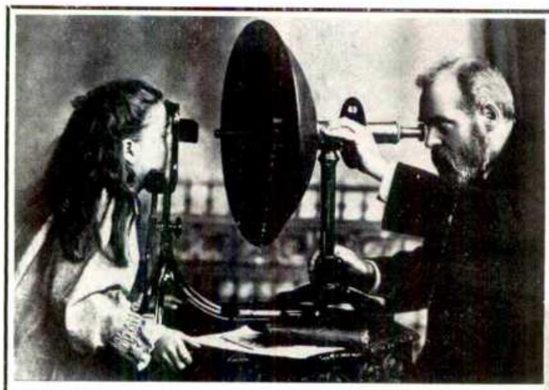

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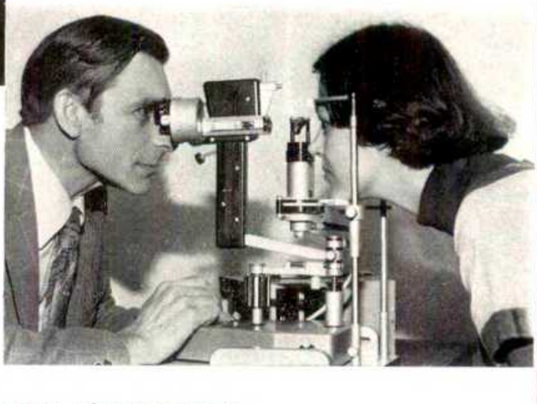

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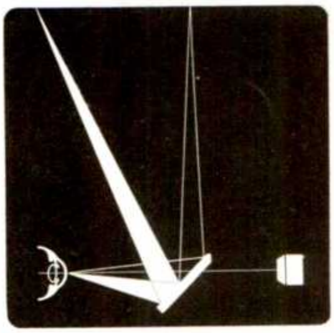

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Bilateral cataract extraction in one session: report on five years' experience*

NISSIM JOSEPH AND ROBERT DAVID

From the Department of Ophthalmology, University of the Witwatersrand, Johannesburg, South Africa

SUMMARY Six hundred and seventy-six patients had both their cataracts removed in one operating session because of the rural and economic conditions of Malawi. These operations were performed over a period of 5 years. The final visual results were satisfactory and the number of complications acceptable in relation to the environmental conditions and medical facilities available. However, the incidence of infection is higher than would be acceptable in a sophisticated medical environment. Three eyes were lost owing to infection, but fortunately in all 3 cases the fellow eye was not affected. Furthermore, broken capsule and vitreous loss occurred more frequently than expected in a sophisticated facility in the eye first operated on. This allowed measures to be taken by the surgeon in many cases to prevent these complications from recurring in the second eye.

With the increase in safety of cataract surgery and the expansion of ophthalmological services to remote places of the world there have been a few encouraging reports in the last 20 years which advocate surgery for bilateral cataracts—under certain circumstances—in one operating session (Chan and De La Paz, 1952; Manschot, 1959; Morax and Pivoteau, 1967; Lugossy, 1968; Jardine, 1972; Suchting, 1973). Simultaneous bilateral cataract extraction is still rather unpopular among experienced ophthalmologists. This is mainly due to fear of postoperative infection, which, should it occur, is still considered to present a danger to both operated eyes. This fear seems to be deeply rooted, since Blaskovicz in the 1930s sharply criticised Elshnig for performing such an 'erratic' procedure (Manschot, 1959). This report presents a large series of simultaneous bilateral cataract extractions, enforced by the circumstances of the ophthalmological services in Malawi, with a constant shortage of hospital beds and long distances to the only eye department where surgery for cataract is available.

Material and methods

In the 5 years between 1 January 1970 and 31 December 1974, 676 patients (1352 eyes) with bilateral cataracts were operated on at the Queen Elizabeth Central Hospital in Blantyre, and both cataracts were removed at one operating session. General anaesthesia was the rule except in those cases in which the patient was considered an anaesthetic hazard. There was no rescrubbing between the operation on the 2 eyes, and only the innermost drape was replaced for the second eye. The operation instruments were not resterilised after the first operation.

The surgical technique employed was as follows: After a conjunctival flap (usually limbal based) was raised, a limbal groove was performed with or without preplaced sutures. After anterior chamber had been opened 1 or 2 peripheral iridectomies were performed. Chymotrypsin was used in patients under 60 years of age. Unfortunately, this drug was frequently unavailable. The lens was delivered with Arruga intracapsular forceps or erysiphake for the first 2 years and mainly with the cryoceps afterwards. Intracapsular extraction was attempted in all cases, and if the capsule ruptured every effort was made to evacuate the remnants, including the posterior capsule. In cases where the anterior vitreous face was broken an anterior vitrectomy was performed, using Weck-cell and iris scissors. Sutures used were either 7·0 or 8·0 virgin silk, usually a total of 8 or 9. The conjunctiva was resutured.

The average operating time for the 2 eyes was 60–70 minutes. An operating microscope was used only during the last year.

Preoperative conjunctival swabs were not routinely taken owing to shortage of laboratory facilities. In the first 2 years all patients received systemic anti-

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*This report is based on the experience of the authors at the Queen Elizabeth Central Hospital in Blantyre, Malawi, while seconded from the Hadassah Hospital, Jerusalem, in the years 1970–71 (R.D.) and 1972–74 (N.J.)

Address for reprints: Dr Robert David, Department of Ophthalmology, Medical School, Hospital Street, Johannesburg 2001, South Africa

biotics for 5 postoperative days, but this was stopped in 1972. The type of antibiotic used depended on availability in the pharmacy and was mainly synthetic penicillin.

Postoperative care included uncovering the more quiet-appearing eye on the first postoperative day and ambulation of patients on the 3rd or 4th day. The patients were discharged 8–12 days after the operation, the time depending on the distance to their villages.

Topical treatment included cycloplegic and chloramphenicol drops and, when necessary, steroids. The medical stores supplied standard spherical +8·00 to +14·00 dioptre sphere glasses free of charge. The glasses, however, were actually given to the patient only on their second or third follow-up visit, usually 2–3 months after surgery. This provided us with a reasonably good follow-up in practically all cases.

There were 494 males and 182 females, a ratio of 2·7:1. The majority of patients (84·9%) were under 70 years of age. The age distribution is seen in Table 1.

Results

VISUAL RESULTS

Four hundred and ninety-four patients (988 eyes) returned for follow-up at least 2 months after surgery. The visual acuity with correction is seen in Table 2. Eighty-six eyes did not regain useful vision, and the ocular pathology in these eyes is seen in Table 3.

OPERATIVE COMPLICATIONS

In a total of 130 eyes (9·6%) the lens capsule broke during delivery, but only in 28 eyes were both eyes of the same patient involved (14 patients). In 67 patients it occurred in the first eye operated on and in 35 in the second eye operated on (Table 4). Loss of vitreous requiring anterior vitrectomy occurred in 90 cataract extractions (6·6%). In 43 patients this occurred in the first eye only and in 25 cases in the second eye only. Eleven patients suffered vitreous loss in both their eyes (Table 4). Expulsive haemorrhage was not seen in any of the operated eyes.

POSTOPERATIVE COMPLICATIONS

Three eyes in 3 different patients had a postoperative endophthalmitis: 1 had bilateral vitreous loss at the time of the surgery, and the eye first operated on became infected 48 hours after the extraction. The second patient had vitreous loss in the left eye, the first eye operated on, and an uncomplicated extraction on the right. The left eye only developed endophthalmitis. The last patient had uncomplicated bilateral surgery, and 48 hours later the right

Table 1 *Age distribution of bilateral cataract patients*

Years	*No.*
≤59	271
60–69	303
70–79	80
≥80	22
Total	676

Table 2 *Visual results in 494 patients (988 eyes)*

Visual acuity	*No.*
<6/60	86
6/36–6/60	194
6/12–6/24	347
≥6/12	361
Total	988

Table 3 *Ocular pathology in 86 eyes with <6/60 vision*

Finding	*Uncomplicated surgery*	*Vitreous loss during extraction*	*Total*
Pre-existing corneal opacity	19	—	19
Corneal oedema	8	9	17
Glaucomatous optic atrophy	14	1	15
Primary optic atrophy	8	—	8
Vitreous haemorrhage (diabetes)	4	3	7
Vitreous haemorrhage (non-diabetic)	3	1	4
Retinal degeneration	6	—	6
Macular hole	3	—	3
Amblyopia	5	—	5
Retinal detachment	—	2	2
Total	70	16	86

Table 4 *Operative complications*

Complication	*Patient 1st eye only (%)*	*Patient 2nd eye only (%)*	*Patient both (%)*	*Total eyes (%)*
Ruptured capsule	67 (4·9)	35 (2·5)	14 (2·0)	130 (9·6)
Broken vitreous	43 (3·1)	25 (1·8)	11 (0·8)	90 (6·6)

Table 5 *Visual results in 56 eyes after vitrectomy*

Visual acuity	*Eyes*
<6/60	16
6/36–6/60	16
6/24–6/12	14
≥6/12	10
Total	56

eye (first operated on) developed endophthalmitis.

Of the 90 eyes with anterior vitrectomy 56 were seen 2 months or more after surgery, and their visual results are shown in Table 5.

Discussion

We did bilateral cataract operations in a single session to meet the problems of a young and developing African country. It was necessary to shorten the patient's time in hospital and ensure a quick turnover to overcome the permanent shortage of beds. Retrospectively, however, there are certain advantages, some of which have already been emphasised by authors advocating this method.

We prefer general to local anaesthesia for cataract surgery, and removing both cataracts in one session saves the patient an additional general anaesthetic.

The fact that either capsule rupture or vitreous loss occurred more frequently in the first eye operated on indicates that these complications were subsequently avoided by some special precaution or modification adopted at the operation on the second eye. A minor detail which triggered the complication in the first eye alerted the surgeon, who could take suitable precautions in the operation immediately following on the second eye. Such a minor detail can be easily overlooked in the operating notes at the time the second eye is subjected to surgery, if this is done at a later date. This is especially true when the second operation is performed by another surgeon.

In the 585 simultaneous cataract extractions reported by Jardine (1972) there were 3 intraocular infections, each affecting one eye of 3 patients. The 3 cases of endophthalmitis in our series also occurred in one eye of 3 patients, while the fellow eye of all these patients remained unaffected.

Anterior vitrectomy is believed to predispose to infection, and this was the case in 2 of our 3 cases. This, however, does not incriminate bilateral surgery, because in 11 patients with bilateral vitreous loss only 1 eye of 1 patient developed an infection.

The relatively high incidence of operative complications such as ruptured capsules and vitreous loss in this series is cause for some concern and comment. It can, at least partially, be attributed to (1) the types of cataract with which our patients presented—frequently hypermature, intumescent, and not uncommonly subluxated; (2) use of the cryoextractor only in the last 3 years and then only on selected cases; and (3) the shortage of chymotrypsin, which was unavailable for various periods.

However, this still leaves unexplained a relatively high incidence (0·22%) of postoperative endophthalmitis. Three eyes out of 1352 operations were lost, fortunately not involving 2 eyes from a single patient. This incidence of endophthalmitis and the possibility that both eyes of one patient could be affected remains the strongest argument against simultaneous bilateral cataract extraction at one surgical session unless there are very cogent social and economic reasons, such as exist in Malawi and many other developing countries.

The ultimate visual result, however, suggests that operating on bilateral cataracts at one session can be an acceptable procedure in certain environmental communities where socioeconomic conditions make it difficult for patients to be readmitted and where medical facilities have to be used sparingly. The patient is saved from double preoperative stress, two general anaesthetics, and time in hospital is shortened. Administrative authorities welcome the economy in operating time, anaesthetic time, hospital beds, and operating theatre expenses.

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Differences and similarities in a series of cases with bilateral intraocular lenses and evaluation of the results

JØRN BOBERG-ANS

From the Charlottenlund Ophthalmological Clinic, Charlottenlund, Denmark

SUMMARY A review is given of the results of intraocular lens implantation in 38 patients, that is, 76 eyes. The observation time was up to 7½ years. Only 5 cases were done as a secondary procedure. The Binkhorst 4-loop lens was preferred. Most of the lenses were fixated with an iris-lens suture. Out of 8 lens luxations 2 were fixed with an iris suture. The final visual acuity and the difference in refraction in spherical as well as cylindrical power are surveyed. The astigmatism and the astigmatic axis are compared in the 2 eyes of each patient. Most of the patients regained stereoscopic vision. It is concluded that neither the lens position, the lens type, the number of iris sutures, nor the number of iridectomies had any influence on the eventual results.

Of 134 patients in my care who had 172 intraocular lens implantations, 38 had bilateral implantations. The follow-up varied from 2 months to 7½ years. Details such as lens position, lens fixation, and number of iridectomies constituted the difference between the eyes. In all cases I was the surgeon, and the surgical technique was fairly constant.

INDICATION FOR INSERTION OF BILATERAL INTRAOCULAR LENSES

Monocular cataracts originally constituted the indication for insertion of intraocular lenses. With the realisation of the safety of intraocular lenses, and owing to the number of patients who had an intraocular lens in 1 eye and an increased lens opacity in the other eye, it was not only natural but also obligatory to insert an intraocular lens in the second eye.

LENGTH OF TIME BETWEEN OPERATIONS (Table 1, Fig. 1)

As Table 1 shows, in 8 of my bilateral cases the length of time between the 2 implants was more than 1 year, in 2 cases more than 4 years, but in 21 cases 6 months or less, and in 9 cases 4 weeks or less. The short duration between the 2 eyes is especially noticeable in the older age group.

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SECONDARY PROCEDURES (Table 2)

In 5 patients lens implantation was performed as a secondary procedure 10 months to 7½ years after a conventional cataract extraction. Having experienced the benefits of an intraocular lens, some patients asked to have a lens inserted as a secondary procedure in the first-operated, aphakic eye. The fate of the secondary implants is seen in Table 2.

A bilateral secondary operation was carried out in only 1 patient. The patients in the other 3 cases of monocular secondary implant were unable to comply with the use of contact lenses or the functional monocularity imposed by cataract glasses. The eventual results suggest that the secondary implantations have not proved to be any exception in the group.

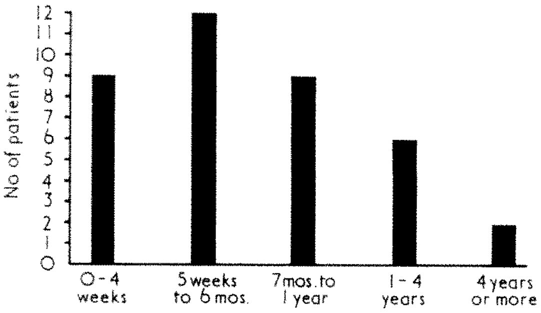

Fig. 1 *Time between operations, 38 patients*

Table 1 *Binocular cases*

	Age in years at time of operation First eye	Time in weeks between implants	Final vision First eye	Final vision Second eye
Under 50 years of age: 8 patients				
	17	36	0·5	0·7
	27	256	1·0	0·7
	28	64	1·0	0·2
	33	80	0·4	0·2
	40	8	1·0	1·0
	44	92	0·9	1·0
	46	12	1·0	1·0
	47	3	0·4	0·7
Average	35	<69	≦0·7	≦0·7
Over 50 years of age: 30 patients				
	51	256	1·0	1·0
	52	3	0·4	0·8
	53	32	1·0	1·0
	53	8	0·2	1·0
	54	60	1·0	0·7
	54	32	0·1	1·0
	55	40	1·0	1·0
	57	1	0·4	0·4
	58	40	1·0	1·0
	59	20	1·0	1·0
	59	96	1·0	1·0
	60	33	0·7	0·5
	61	1	1·0	0·9
	62	44	1·0	0·6
	64	1	1·0	1·0
	64	4	1·0	0·8
	64	28	0·7	1·0
	64	177	0·2	0·1
	66	4	1·0	1·0
	67	8	0·9	1·0
	68	28	0·2	1·0
	69	13	1·0	1·0
	69	8	0·2	0·4
	70	1	0·9	0·8
	71	22	1·0	1·0
	72	24	1·0	0·9
	72	8	0·8	0·7
	75	8	0·9	0·6
	80	4	0·4	0·1
	82	20	0·8	0·1
Average	63½	34	≦0·7	≦0·8

Even though the final results of the secondary implants are good, I am not in favour of exposing a good surgical result to the hazards of another surgical procedure, but I admit that in special cases it may well be justified.

TYPES OF LENSES

Four Worst lenses have been used with a Binkhorst 4 loop lens in the other eye. Two Fedorov lenses have been used with a Binkhorst 4 loop lens as well as 18 Binkhorst 4 loop lenses with the Lurie modification of the black posterior loop. These have been used in combination with another type of lens in the other eye, except in 4 patients in whom both eyes have a Lurie lens.

POSITION OF LENS

Twenty eight lenses have been placed in the horizontal position, 15 in the oblique position, and 29 in the vertical position. Only in 13 cases has the position of the lens been the same in both eyes.

The types of lenses used and the position of the lens have had no influence on the condition of the cornea, the postoperative course, or the final visual acuity.

IRIS-LENS SUTURES

In the first 12 cases iris-lens sutures were not routinely used. In the following cases I varied the insertion of the iris-lens suture in the 2 eyes: no suture, 1 suture, 2 sutures, and transiridectomy suture. This variation in technique has not had any detectable influence on the condition of the cornea, the iris, or the duration of the postoperative irritation (Fig. 2). However, without any proof I have the impression that the transiridectomy sutures cause a slightly more intense reaction in the first few postoperative days. It is difficult to ascertain whether the suture in the iris has actually perforated the pigment layer or not, but I have the impression that the least irritation is found when the nylon suture is placed inside the iris stroma without perforation of the pigment epithelium.

Table 2 *Secondary implants*

Patient born	M	F	R	L	Vision after cataract extr.	Eventual vision after lens implant
41	X		X		1·0	1·0→0·2 (2 grafts)
41				X	1·0	1·0
09		X		X	0·7	1·0
10		X	X		1·0	0·8
03		X		X	1·0	1·0

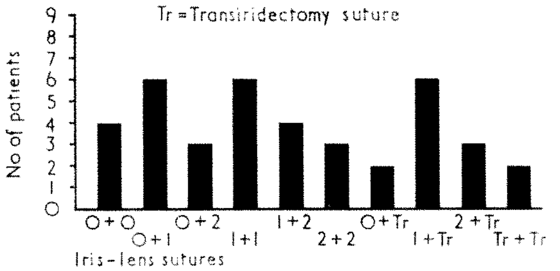

Fig. 2 *Number and type of iris-lens sutures in the 2 eyes of 38 patients*

NUMBER OF IRIDECTOMIES (Fig. 3)
Variation in the number of iridectomies has also been examined in relation to postoperative tension and eventual results, but no associations have been found.

LENS LUXATION (Table 3)
Lens luxation has occurred 8 times in 7 eyes; 1 eye had a luxation twice. Luxation has occurred in 2 eyes in which the lens had been fixated with a suture. Three eyes have had fluid vitreous. In 1 patient 1 eye with a Worst Medallion lens sutured to the iris luxated with the nasal loop into the anterior chamber. In the other eye the lens, which had been inserted as a secondary procedure with no iris suture, luxated with both anterior loops behind the iris. In both of these cases surgical repositioning was required.

While it may be possible to reposition the unsutured lenses medically by dilating the pupil, it has not been possible to do so with the lenses fixated with a suture to the iris.

Significant *vitreous opacities* have not appeared in any of the cases.

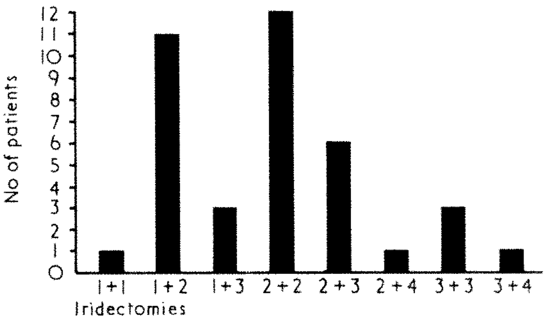

Fig. 3 *Number of iridectomies in the 2 eyes of 38 patients*

RETINAL OEDEMA (Table 4)
Five eyes in 4 patients have had central transient retinal changes 12 to 128 weeks postoperatively. Four of the eyes regained their vision 58 to 124 weeks postoperatively. One of the retinal changes in a 60 year old male appeared 128 weeks (2½ years) postoperatively. Fluorescein angiography did not disclose the aetiology. The changes encountered in the other cases retained an oedematous appearance which decreased slowly when the vision returned. Only 1 of the patients had a bilateral transient retinal change, but as he has diabetes he should be excluded from these considerations. Fluorescein angiography pointed to an Irvine-Gass syndrome in the left eye, but not in the right eye. It is interesting to note that 1 eye in each of the other patients has not had any retinal disease. I would like to take this fact as a hint that the presence of the intraocular lens has not been responsible for the changes encountered.

Table 3 *Subluxations*

Patient born	*Type of lens*	*Iris suture*	*Time after operation*	*Treatment*
19	Binkhorst-Lurie	0	3⅝ years	Medical
27	Binkhorst-Lurie	0	2 years	Medical
27	Binkhorst-Lurie	0	2½ years	Medical
17	Binkhorst-Morcher	0	4¼ years	Medical
20	Binkhorst-Morcher	0	8 months	Surgical
09	Worst	1	3 years	Surgical
09	Binkhorst-Morcher	0	2 weeks	Surgical
95	Binkhorst-Morcher	1	3 days	Surgical

Table 4 *Transient retinal changes*

	Postop. vision		*Decreased vision*		*Weeks postop*		*Regained vision*		*Weeks postop.*		
Patient born	*first eye*	*second eye*	*first eye*	*second eye*	*first eye*	*second eye*	*first eye*	*second eye*	*first eye*	*second eye*	*Not regained*
43	1·0	0·9		1/60		44		0·7		84	
16	0·9	1·0	0·3		128						X
13	1·0	1·0		0·6		28		1·0		124	
20	1·0	1·0	0·5	0·3	16	20	1·0	0·5	69	58	

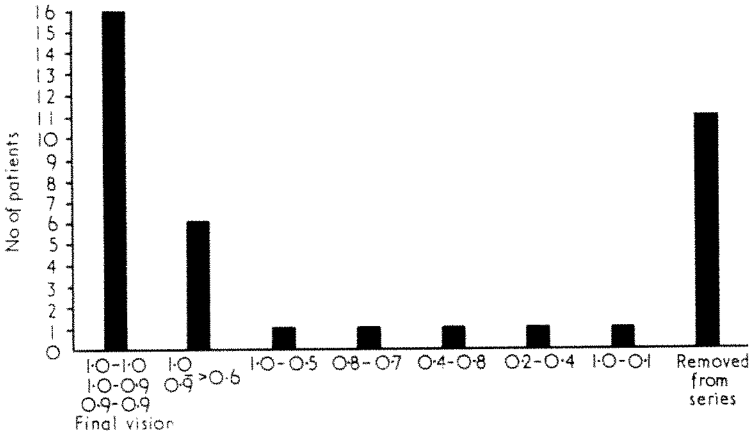

Fig. 4 *Final visual acuity, 38 patients*

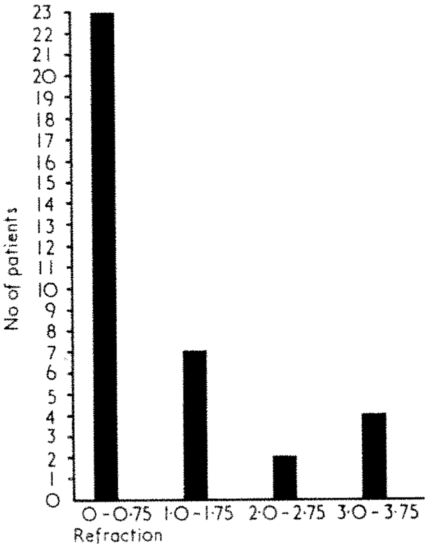

Fig. 5 *Difference between refraction in the 2 eyes of 36 patients*

IRITIS

One patient, 52 years of age, has had an iritis of equal severity in both eyes between 8 and 12 weeks postoperatively. The length of time between the operation on the 2 eyes was 21 days. Apart from a cold and the fact that she works in a dry cleaners, no special aetiology has been found.

FINAL VISUAL ACUITY (Fig. 4)

Owing to special conditions (corneal changes, glaucoma, amblyopia, pigmentary retinopathy, and senile degeneration) 11 patients have been excluded from the evaluation of the final visual acuity and refraction.

From the table of final visual acuity, it appears that 45% have acquired a visual acuity of 1·0 or 0·9 in both eyes, 16% have acquired a vision of 1·0 or 0·9 in 1 eye and better than 0·6 in the other eye; 3% (i.e., 1 patient) is represented in each of the three columns: 1·0 and 0·5, 0·8 and 0·7, and 0·4 and 0·8. That is, 9% have acquired a good vision in 1 eye and a usable vision in the other eye, while 1 patient acquired a vision of 0·2 and 0·4 and another patient 1·0 and 0·1.

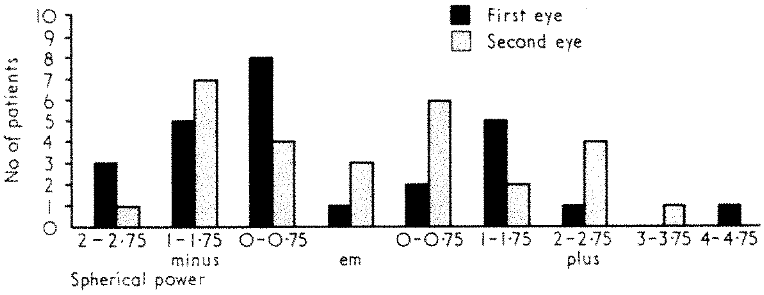

Fig. 6 *Total value of spherical power in first and second eye, 54 eyes; 1 D sph = ½ D cyl*

The former of these 2 patients was born in 1905 and has a senile degeneration in both eyes. The latter has a senile degeneration in only 1 eye.

DIFFERENCE IN TOTAL REFRACTION IN BOTH EYES (Fig. 5)

If it is presumed that a 1·0 cylinder equals close to 0·5 spherical, the difference in total refraction between the 2 eyes has been estimated, as seen from the chart. Thirty of the patients have had less than 2 dioptres' difference and 23 have had less than 1 dioptre's difference between the 2 eyes.

TOTAL SPHERICAL POWER (Fig. 6)

From the value of total spherical power of the first and second eye (1 cylinder equals approximately 0·5 spherical) it appears that 4 eyes have obtained emmetropia, 8 have obtained a spherical refraction of less than +1·0, 15 have less than +2·0, 12 have less than −1·0, and 24 have less than −2·0. As intended, the major part of the eyes have attained a slight myopia.

DIFFERENCE IN CYLINDER IN THE FIRST AND SECOND EYE (Fig. 7)

Difference in cylinder between the 2 eyes is in 15 cases less than 0·5 dioptres and less than 1 dioptre in a total of 26 cases. In 9 cases there is a difference of 2 to 3 dioptres and in only 1 case a difference of 4 dioptres.

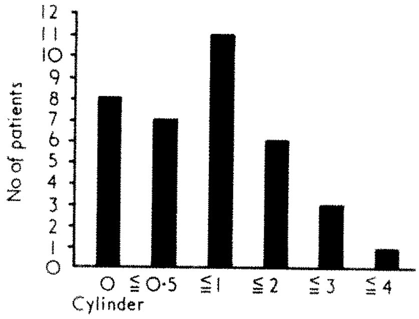

Fig. 7 *Difference in cylinder, 36 patients*

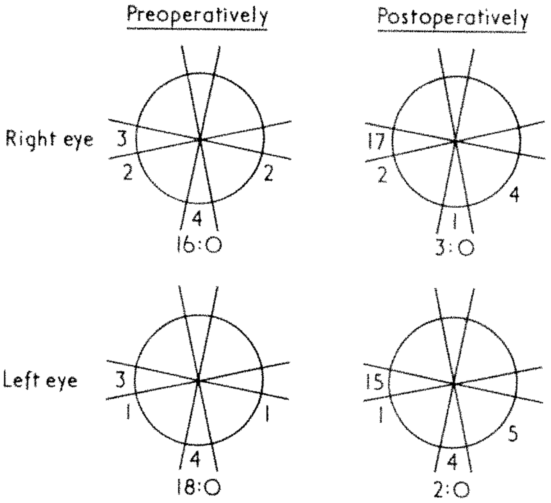

Fig. 9 *Astigmatism preoperatively and postoperatively, 27 patients. 16+18=34 eyes had no astigmatism preoperatively; 3+2=5 eyes had no astigmatism postoperatively*

VALUE OF CYLINDER POWER IN THE FIRST AND SECOND EYE (Fig. 8)

The value of cylinder power shows that 15 eyes have less than 1 dioptre, 42 eyes have less than 2 dioptres, and 18 have between 2·5 and 4·5 dioptres. This indicates that the surgical technique has been fairly constant.

AXIS OF ASTIGMATISM (Fig. 9)

It appears that while 81·41% had no astigmatism preoperatively, 9·2% had no astigmatism postoperatively. 11·1% had astigmatism against the rule preoperatively in relation to 59·3% postoperatively.

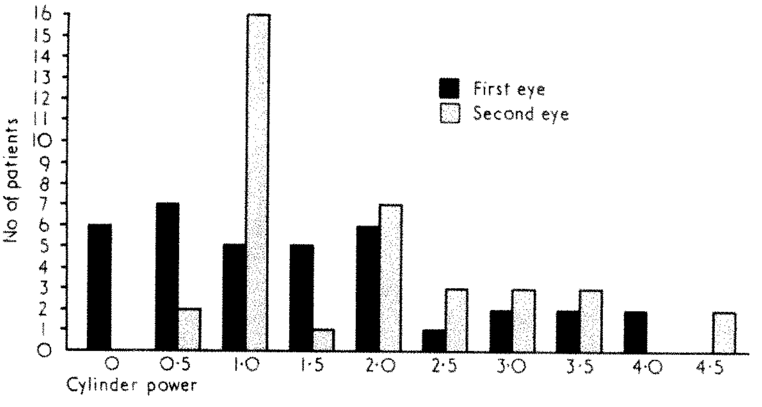

Fig. 8 *Value of cylinder power in first and second eye, 64 eyes*

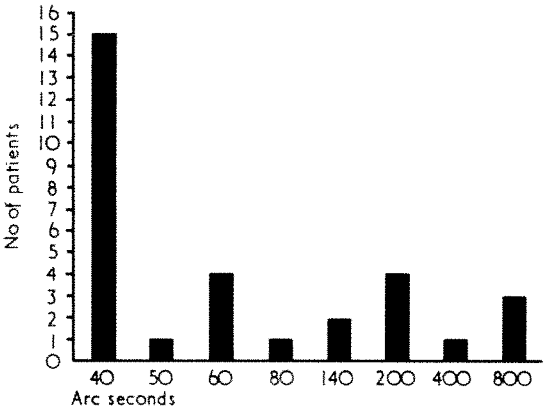

Fig. 10 *Titmus stereoscopic test, 31 patients*

15% had preoperative astigmatism with the rule while 9·2% had astigmatism with the rule postoperatively. 11·1% had oblique astigmatism preoperatively while 22·2% had oblique astigmatism postoperatively. Thirty-six eyes, or 66·6% of the astigmatism, was less than 1·5 and 90% less than 2·0 dioptres.

In conclusion it can be stated that the corneal curvature changes after a cataract extraction in the usual way from slightly with the rule to slightly against the rule. The amount of astigmatism created has in most cases not been more than 2 dioptres. There has been no significant difference between the axis of the astigmatism in the right and the left eye. The presence and position of the lens has had no influence on the amount of astigmatism or the axis.

TITMUS STEREOSCOPIC TEST (Fig. 10)

As Fig. 10 shows, 20 patients have a stereoscopic appreciation of 60 arc seconds or better, and 65% have completely regained their stereoscopic vision. Those who have less stereoscopic appreciation have not achieved equal vision or a vision better than 0·5.

DIPLOPIA

None of the patients in this series has complained of diplopia.

Conclusion

It seems justifiable to conclude that neither the position of the lens, the type of lens used, the number or position of iris-lens sutures, nor the number of iridectomies has had, in this series, any influence on the conditions of the cornea, iris, or eventual function of the eyes in the same patient. The similarity of the results obtained in the 2 eyes of the same patient is striking. The good stereoscopic appreciation achieved is noteworthy.

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Aphakic macular oedema: a two-year follow-up study

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SUMMARY A 2-year follow-up study was carried out on patients known to have developed aphakic macular oedema 6 weeks postoperatively, and the results were compared with those in a control group who had not developed oedema. Four eyes (12%) still had macular oedema, the visual acuities ranging between 6/5 and 6/9. There was no significant difference in visual acuities at 2 years between the 2 groups of patients. Visual acuity had significantly improved between 6 weeks and 2 years in the eyes that had macular oedema at 6 weeks after extraction. Factors causing persistence of aphakic macular oedema are discussed.

Macular degeneration following cataract extraction was described by Irvine (1953). Gass and Norton (1966) described perifoveal capillary leakage of fluorescein and aphakic macular oedema in patients referred because of a fall in visual acuity noted 4 to 12 weeks after cataract extraction. Prospective studies indicated that aphakic macular oedema occurred in 40% (Irvine *et al.*, 1971), 50% (Hitchings *et al.*, 1975), and 60% (Yoshioka and Kawashima, 1971) of patients, many of whom maintained good vision.

Gass and Norton (1969) showed that in patients referred with visual loss from this condition the oedema settled within 6 months in 50% and persisted for 3 years in 8%. In a prospective study Hitchings *et al.* (1975) showed that at 6 months resolution had occurred in 57% and decreased fluorescein leakage in 28%, while 15% where unchanged or worse.

This paper reports the results of a 2-year follow-up study on patients who participated in a prospective study of the incidence of aphakic macular oedema (Hitchings *et al.*, 1975) and assesses the effects of macular oedema on visual acuity and macular appearance.

Materials and methods

All patients who participated in the original study were asked to return for a full ophthalmic examination. They had undergone cataract extraction 2 to 2½ years before. Examination included refraction, slit-lamp biomicroscopy of the anterior and posterior segment, and colour and fluorescein photography. The angiographic technique employed was the standard technique used at Moorfields Eye Hospital (Teeters and Bird, 1973).

Results

Seventy-one patients were asked to return. Seven patients had died, 2 were too ill to attend, and 1 had developed a rhegmatogenous retinal detachment in the follow-up period. Six patients could not be traced. Fifty-five patients, 57 eyes (of which 33 eyes had shown aphakic macular oedema at 6 weeks postoperatively) attended for the follow-up study.

Aphakic macular oedema was observed in 4 eyes, the visual acuities being 6/5, 6/6, and 2 eyes with 6/9. A comparison of visual acuities 6 weeks and 2+ years for each of these eyes is seen in Table 1. It will be seen that acuity had improved in each eye.

A comparison of visual acuities at 6 weeks and 2 to 2½ years after lens extraction of patients who did and did not show fluorescein leakage at 6 weeks is seen in Figs. 1 and 2. It will be seen that, while at 6 weeks the mean visual acuity is 6/7·5 and 6/6 respectively for the eyes that did and did not show fluorescein leakage, at 2+ years the mean visual acuity is virtually the same, at 6/6 for the 2 groups. Chi-square analysis demonstrated a significant difference in visual acuity at 6 weeks and 2+ years in those patients' eyes that developed aphakic macular oedema ($P<0.05$) but no significant difference over the same period for the eyes that did not. Nor was there any significant difference between the 2 groups at 2 weeks or 2+ years. It will be noted that 4 of the eyes had visual acuities of less than 6/18 because of 1 eye each with amblyopia, marked postoperative astigmatic error, retinoschisis

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Table 1 *Visual acuities and complicating features in eyes with aphakic macular oedema 2 to 2½ years after operation*

Eye No.	*VA at 6 weeks*	*VA at 2 to 2½ years*	*Complication*
1	6/6	6/5	Heterochromic cyclitis
2	6/12	6/6	—
3	6/24	6/9	Persistent flat anterior chamber
4	6/12	6/9	Vitreous loss

affecting the macula, and congenital cataract. These patients have not been included in the calculations of mean visual acuity.

The anterior hyaloid face had ruptured in 29 eyes, of which 15 had shown aphakic macular oedema 6 weeks postoperatively. No patient had inflammatory cells in the vitreous.

Fine granular pigmentation in the macular region was seen in 10 eyes, of which 9 had shown leakage of fluorescein. One eye known to have developed aphakic macular oedema now had disciform degeneration affecting the macular region. Multiple drusen at the posterior pole were noted in 2 eyes not known to have developed aphakic macular oedema. The appearances of the macular region at 2 to 2½ years after extraction is summarised in Table 2.

Discussion

On the basis of the patients described aphakic macular oedema is a common sequela of uncomplicated cataract extraction (Hitchings *et al.*, 1975). Characteristic features are a fall in visual

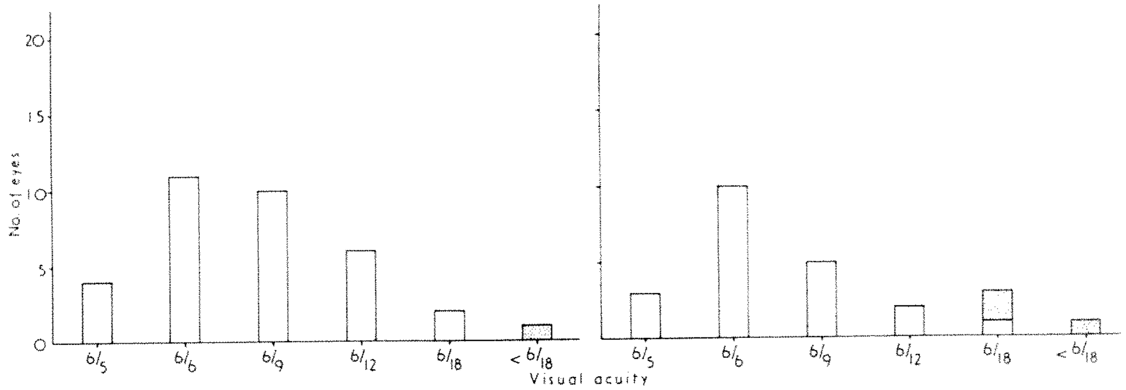

Fig. 1 *Comparison of visual acuities at 6 weeks in eyes with and without cystoid macular oedema at 6 weeks after cataract extraction. NB: Stippling denotes eyes not included in calculation of mean visual acuity—see text*

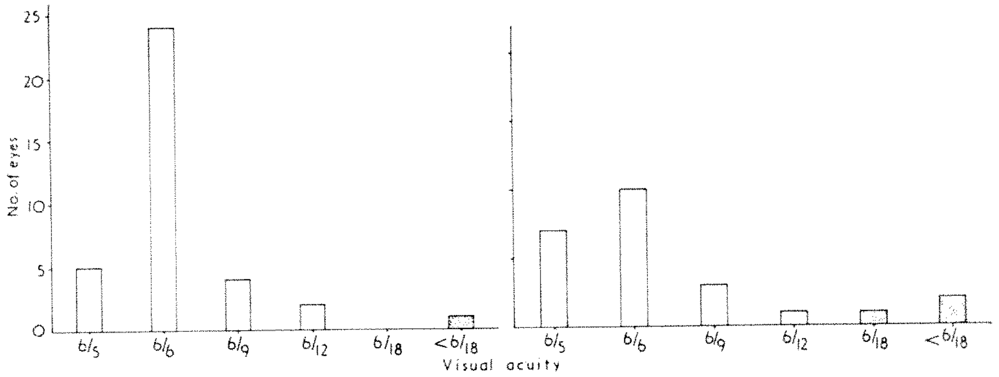

Fig. 2 *Comparison of visual acuities at 2 to 2½ years in eyes with and without cystoid macular oedema at 6 weeks after cataract extraction. NB: Stippling denotes eyes not included in calculation of mean visual acuity—see text*

Table 2 *Appearance of the macular region 2 to 2½ years after extraction*

A. Eyes never shown to develop oedema	*No. of eyes*	*B. Eyes shown to have oedema at 6 weeks after operation*	*No. of eyes*
Pigmentary stippling	1	Pigmentary stippling	9
Retinoschisis affecting posterior pole	1	Disciform degeneration	1
Macular drusen	2	Macular oedema	4

acuity or a failure to achieve expected levels of visual acuity in the immediate postoperative period. Biomicroscopy reveals cells in the posterior vitreous and a loss of foveal reflex; cystoid intraretinal spaces may be seen in the macular region. Fluorescein angiography reveals intraretinal accumulation of fluorescein in a 'petalloid' pattern.

The aphakic macular oedema seen in the patients reported here appeared to undergo spontaneous resolution. Fluorescein leakage completely ceased by 6 months in 16 of the 29 eyes studied (Hitchings *et al.*, 1975). Four eyes (12%) of those showing macular oedema at 6 weeks after extraction still had macular oedema at 2 to 2½ years. In 3 of these eyes fluorescein angiography at 6 months showed macular oedema. No other factor considered likely to be responsible for the macular oedema was identified. Specifically, no patient had been receiving topical adrenaline therapy (Michels and Maumanee, 1975), and no eyes had evidence of a retinal vein occlusion, diabetic retinopathy, or posterior segment inflammation. Complications identified for the eyes with persistent aphakic macular oedema are shown in Table 1. Similar complications, however, occurred in patients in whom oedema was never detected.

Perifoveal pigmentary stippling was the only visible change found preferentially in eyes known to have aphakic macular oedema. Gass and Norton (1969) noted 'pigment mottling' in the macular region after resolution of aphakic macular oedema. In our patients this morphological change did not appear to affect the visual acuity.

The mean visual acuity for the eyes known to have developed aphakic macular oedema improved, so that by 2 to 2½ years there was no significant difference between eyes known to have and not to have developed macular oedema. Visual acuities ranging from 6/5 to 6/9 were obtained in the 4 eyes with persistent macular oedema. In these eyes prolonged oedema was compatible with good acuity, perhaps because none had developed irreversible structural changes, noted by Gass and Norton (1969). The good acuity seen with persistent macular oedema is in marked contrast to the poor acuity seen in eyes with macular oedema associated with a central or branch vein occlusion or diabetic retinopathy. These contrasting visual acuities may reflect a difference in composition of the oedema fluid and/or the adequacy of retinal nutrition.

In most instances aphakic macular oedema is transient, producing little if any long-term effect on vision. The condition is important when the oedema is prolonged; intraretinal structural changes with decreased acuity may eventually occur (Gass and Norton, 1969). Factors causing development and then persistence of aphakic macular oedema still remain obscure. While aphakic macular oedema is a common sequel to uncomplicated cataract extraction, its persistence may reflect a non-specific retinal response to a variety of stimuli. It must be assumed that an unidentified factor or combination of factors caused aphakic macular oedema to persist over a 2-year period in these eyes.

I thank consultants at Moorfields Eye Hospital for allowing me to study patients under their care. I thank Mr A. C. Bird for helpful discussion, Mr H. Donovan for statistical analysis, and Miss E. Nightingale, who typed the manuscript.

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Review of Binkhorst intraocular lenses

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SUMMARY Experience is described of 150 cases in which an intraocular lens of the Binkhorst (iris clip and iridocapsular type) was introduced after cataract extraction. The most serious complications are dislocation and corneal dystrophy.

Replacement of the cataractous lens by an intraocular device dates back from the work done by Harold Ridley (1951). Others (Strampelli, Choyce, Binkhorst, Worst, Dannheim, Federov, and Copeland) followed, modifying the type of lens used.

Interest in these optical devices remained because of the great advantages gained—for example, good visual field and the refractive state of the eye approaching the normal (Hall, 1974; Percival and Yousef, 1976). (The power of the correcting glasses is minimal.) So far over 200 intraocular lenses of the Binkhorst types have been inserted in this unit.

This paper deals with the first 150 of these. The cataractous lens was replaced by the Binkhorst clip lens type of pseudophakos (117 cases) and the Binkhorst iridocapsular lens type of pseudophakos (33 cases) (Binkhorst, 1973). These 150 cases were not selected in any way. The operations were performed when an intraocular lens became available, and the next person on the waiting list for cataract surgery was chosen. The use of these lenses in this study started in December 1970, when the first lens was inserted, and the last lens in this series was introduced on 9 November 1975. The longest period of observation is consequently nearly 6 years and the shortest period is 6 months. These dates are important in the evaluation of the results. Excluded from the series were patients (11 eyes) who died before they could be followed up for 6 months or who did not attend for follow-up.

Patients and methods

VISUAL RESULTS

Apart from eyes with badly injured corneae due to trauma and those with retinal disease the corrected visual acuity was 6/12 or better in 80% of eyes.

OPERATIVE TECHNIQUE

Nearly all the operations were done under local anaesthesia unless the patient specially requested general anaesthesia or was unable to co-operate.

A limbal section nearly 180° with limbus-based conjunctival flap was the usual procedure. A Flieringa ring was often used fastened to the sclera by at least 12 sutures, and the corneal incision was closed with a minimum of 4 virgin silk sutures. Initially air was used to reform the anterior chamber, but latterly saline. Zonulysin was used in all but the extracapsular operations, and some of the extracapsular extractions were also fitted with the iris clip lens when it was thought that insufficient capsule had remained to use the iridocapsular lens with safety from dislocation.

COMPLICATIONS

(*a*) *Dislocation of lens* (4 cases). Initially dislocation of the lenses was feared and the patients were maintained on 2% pilocarpine drops 3 times a day. However, a number of eyes developed a thin membrane in the pupil, and further miotic treatment to retain the lens in place was not necessary. A special paper deals with these 4 dislocated lenses.

(*b*) *Deposit on lens*. Some lenses showed a deposit of what can best be described as mutton fat keratic precipitates. The cornea was not involved and the visual acuity did not seem to be affected. These deposits may be due to accumulation of cells and exudates on the pseudophakos as a result of static electricity.

(*c*) The most serious complication was *corneal dystrophy*. We found 2 types of dystrophy, localised and general.

Localised dystrophy

This classification (an alternative term is localised endothelial decompensation) (Binkhorst, 1973) was made when the corneal oedema was confined to a

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small localised area of the cornea only. These eyes did not have their pseudophakos removed, and the visual acuity remains good. We found 10 cases of this kind and all in eyes fitted with iris clip lenses.

General dystrophy
This classification (alternative term generalised endothelial decomposition) (Binkhorst, 1973) was made when the whole of the cornea was involved with perhaps some clear areas. We found 16 cases of this kind. Two of these had an iridocapsular lens, and the other 14 had been fitted with an iris clip lens. All these cases have had the pseudophakos removed at a subsequent operation. These cases of corneal dystrophy warrant further comment.

Onset—Binkhorst (1973) mentions that all cases of corneal dystrophy in his series developed immediately after surgery. In our series of 16 cases of generalised corneal dystrophy there was great variation in the time of onset of the dystrophy: 2 cases developed dystrophy after 4 years; 2 cases developed dystrophy after 2 months. In the other eyes the dystrophy had its onset between 1 and 3 years.

Possible causes (considering the 16 eyes with generalised corneal dystrophy only)—We found 2 *diabetics* among the 16. In view of the fact that 5 of the 16 started off with badly traumatised cornea, the incidence of 2 out of 11 (18%) is extremely high.

One patient with corneal dystrophy suffered from polycythaemia vera. One other patient suffered rom chronic bronchitis, emphysema, gout, and congestive heart failure. One eye had an unintentional filtering bleb covered by conjunctiva. In many of the other cases there had been contact between the cornea and the lens initially, though subsequently there seemed to be no problem.

Looking back at these cases it seems to me that some of these corneal dystrophies could have been prevented by removing the pseudophakos in time and by excluding cases with the above diseases. Slit-lamp examination to observe the endothelium is now done in all eyes in which introduction of an artificial lens is planned.

Type of lens—If one considers the total number of 26 eyes with localised and general corneal dystrophy, then the ratio between iris clip and iridocapsular lenses is 24:2 or 12:1, respectively. Of the total of 150 eyes studied the ratio of clip lenses to iridocapsular lenses is 3½:1. It follows, therefore, that corneal dystrophy is about 3 times more common when an iris clip is used than if the iridocapsular lens is used. This, however, may be caused by numerous other factors. Three obvious ones spring to mind: (1) The younger age group in which the iridocapsular lens is used in contrast to the older age group in the iris clip type. (2) The different kind of operations: the iris clip lens used with mainly intracapsular lens extractions (but also in some extracapsular lens extractions). The iridocapsular lenses used exclusively with extracapsular lens extraction. (3) The use of Zonulysin exclusively when the iris clip lens is used.

There may be numerous other factors. Van Balen *et al.* (personal communication) and Binkhorst (1973) think that contact between anterior loop and endothelium plays a role. This may be so in some cases, but I do not think this is the main cause. Corneal dystrophy also occurred in 2 eyes with an iridocapsular lens, where anterior loop contact is excluded.

Since corneal dystrophy in our series had its onset even 4 years after lens implantation, we expect further cases of corneal dystrophy in the present series. The percentage of corneal dystrophy, if one includes localised dystrophy, is high, namely 26 out of 150 (17%).

However, it is difficult to compare series. Our cases were not selected, and 5 serious corneal perforating injuries were fitted with these lenses (the lenses had to be removed eventually). If these 5 cases are subtracted from the 16 with generalised corneal dystrophy one arrives at a figure of 7 to 8%, which is in keeping with the results of the Rotterdam University Eye Clinic (Van Balen *et al.*, personal communication). Yet the percentage of dystrophies in this present series might rise if patients live long enough and when the follow-up time is increased.

Postoperative iritis—This occurred in a minority of cases. The exact number is not known because a definite diagnosis of iritis after operation is difficult to make. By definition inflammation (response to injury) is always present in any eye after operation; posterior synechiae are difficult to form, and a flare in the anterior chamber is often seen after any trauma; exudate on the endothelium may be lens matter. Postoperative routine steroid drops (with antibiotics) were given. They may be a factor in the low incidence of postoperative iritis. This complication never gave rise to anxiety, though the pupil cannot be dilated.

Secondary glaucoma—Again this is not always easy to evaluate. Fear of infection excludes tonometry in the early stages. One eye with iridocapsular lens needed a filtering operation (Stallard's) and shows localised corneal dystrophy (included in the series). There is a broad sheath of anterior synechiae in this eye probably caused by pressure of the posterior loop, since these synechiae overlie the position of the posterior loop (Pearce, 1972; Smith and Anderson, 1976). Apart from the above case we encountered only temporary rises of intraocular pressure which did not cause anxiety. It must be remembered that pilocarpine 2% drops were given routinely to retain the lens in place, and therefore possible glaucoma was already being treated medically. One bonus of the pseudophakos may even lie in the fact that possible glaucoma (unrelated to the pseudophakos) is being treated prophylactically.

Retinal detachment.—Needling is often necessary (not only in extracapsular extractions) and slightly more difficult in that one has to introduce 2 knife needles between pupil and lens. The use of Flieringa's ring (this time fastened to the sclera by only 5 or 6 sutures) is most helpful for fixation of the eye.

It is all the more striking, therefore, that we had only 1 case of retinal detachment. The vitreous does seem to have support from the pseudophakos.

REMOVAL OF THE PSEUDOPHAKOS

We have removed 23 lenses, 21 of the iris clip type and 2 of the iridocapsular type. The reasons are as follows: 4 lenses had dislocated, all of the iris clip type; 16 because they caused corneal dystrophy; 2 because of persistent pain, and in 1 of these there was direct contact between the iridocapsular lens and the cornea as well, so that corneal dystrophy was feared; 1 pseudophakos was removed because there was contact between the lens and the cornea but there was no pain—at least yet.

OPERATIVE TECHNIQUE

Apart from removal of dislocated lenses, which technique is described elsewhere, the removal of pseudophakos of the clip type is straighforward. Flieringa's ring (fastened to the sclera by at least 12 sutures) was always used. The pupil was semidilated just before surgery. A limbus type of incision with limbus-based conjunctival flap was made, and 1 set of anterior loops was grasped by iris forceps. The iris was pulled off the corresponding posterior set of loops and the lens removed. Sometimes before this manoeuvre the pseudophakos was rotated by anterior synechiae spatula so as to lie vertical. The above procedure was facilitated thereby.

The removal of iridocapsular lenses can be much more difficult, since adhesions form between the loops and capsule. Vannas scissors are helpful in cutting the posterior loops from the capsule remnant.

STATE OF VITREOUS

The introduction of an intraocular lens is not always possible. Whether it is depends on the state of the vitreous. Vitreous loss by itself is thought to be a contraindication for the introduction of a lens, but 1 case in which vitreous loss occurred and in which an iris clip lens was nevertheless introduced showed a visual acuity of 6/9 with correction, and there were no complications. It is not, however, recommended by Binkhorst (1973).

My thanks are due to Dr A. M. Chowdhury and other members of the staff of this department; also to Professor Van Balen, Rotterdam University Eye Clinic, who operated on the first 2 eyes to show us his technique.

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British Journal of Ophthalmology, 1977, **61**, 634–636

Outflow changes in positive provocative tests

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SUMMARY The outflow changes in 26 eyes were measured during the course of a positive provocative test with pilocarpine and phenylephrine. Three separate patterns of response occurred: (1) One dose of pilocarpine and phenylephrine produced an acute attack with a large reduction in outflow. (2) The first dose of pilocarpine and phenylephrine produced a fall in pressure and increase in outflow. The second dose reversed this effect and closed the angle. (3) The first dose of pilocarpine and phenylephrine increased pressure by an insignificant amount and decreased outflow. The second dose accentuated this response and produced an acute attack.

The effect of pilocarpine and phenylephrine drops instilled simultaneously into eyes at risk of developing closed-angle glaucoma is to produce a significant pressure increase (greater than 8 mmHg) in 60 to 70% (Mapstone, 1976). The purpose of this paper is to describe the changes in outflow facility that occur during a positive provocative test.

Material and methods

The provocative test is conducted as follows: At zero hours the intraocular pressure was recorded, outflow facility measured and pilocarpine drops 2% plus phenylephrine drops 10% were instilled. Subsequently at approximately half-hourly intervals, phenylephrine 10% was instilled and the intraocular pressure recorded. As soon as pressure had increased significantly (greater than 8 mmHg) the outflow facility was measured and the test terminated by thymoxamine drops ½% and intravenous acetazolamide 500 mg.

If after the lapse of 1½ hours from the start there had been no significant increase in pressure, the pressure was recorded, facility of outflow measured, and a further dose of pilocarpine drops 2% and phenylephrine drops 10% instilled. One hour later (that is 2½ hours from the start of the test) if there was no significant increase in pressure the test was terminated by the instillation of thymoxamine drops ½%. If there was a significant increase in pressure the facility of outflow was measured and the test terminated with thymoxamine drops ½% and intravenous acetazolamide 500 mg.

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The material consists of 26 eyes from 26 patients who had closed-angle glaucoma in the contralateral eye and a positive provocative test. Negative test results are not described or discussed in this paper.

Results

Three different patterns of response occurred:

(1) Twelve of the 26 eyes developed a positive provocative test after 1 dose of pilocarpine and phenylephrine. The mean values are recorded in Fig. 1 and show that pressure increased from a mean of 16 mmHg to a mean of 35·1 mmHg 67 minutes after the start of the test. At the same time the facility of outflow (C) decreased from a mean of 0·21 to a mean of 0·05.

(2) In 7 eyes the first dose of pilocarpine and phenylephrine produced a fall in pressure and an increase in C, whereas the second dose of pilocarpine

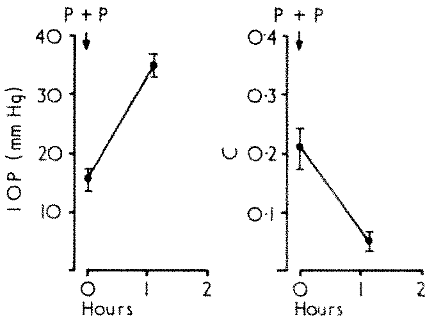

Fig. 1 *Response of 12 eyes to provocative testing with pilocarpine and phenylephrine, one dose is sufficient to produce an acute attack. Mean values and standard error recorded. P + P = Pilocarpine and Phenylephrine*

and phenylephrine produced an opposite response. Fig. 2 records the results and shows that after the first dose of pilocarpine and phenylephrine pressure fell from 19·7 to 16·4 mmHg and C increased from 0·17 to 0·27; 55 minutes after the second dose of pilocarpine and phenylephrine pressure increased from 16·4 to 32·7 mmHg and C decreased from 0·27 to 0·02.

(3) In the remaining 7 eyes the first dose of pilocarpine and phenylephrine produced an increase in pressure and a decrease in C, changes which were accentuated by the second dose of pilocarpine and phenylephrine. Fig. 3 records the results and shows that after the first dose of pilocarpine and phenylephrine pressure increased from 14·9 to 16·6 mmHg and C decreased from 0·24 to 0·14; 74 minutes after the second dose of pilocarpine and phenylephrine pressure increased from 16·6 to 40 mmHg and C decreased from 0·14 to 0·02.

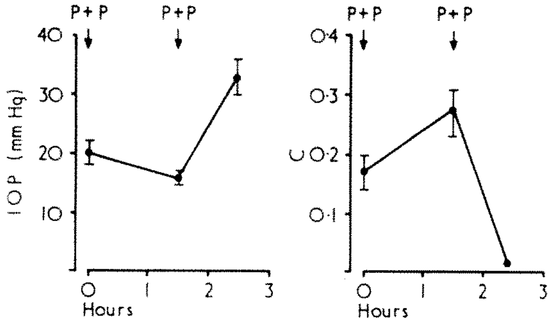

Fig. 2 *Response of 7 eyes to provocative testing with pilocarpine and phenylephrine; the first dose decreases pressure and increases C. The second dose has an opposite effect. Mean values and standard error recorded. P+P = Pilocarpine and Phenylephrine*

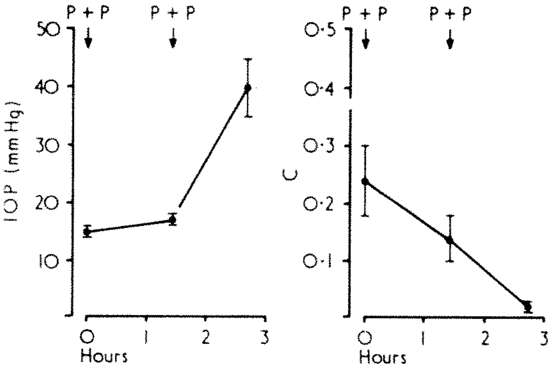

Fig. 3 *Response of 7 eyes to provocative testing with pilocarpine and phenylephrine; the first dose increases pressure and decreases outflow, a change accentuated by the second dose. Mean values and standard error recorded. P+P = Pilocarpine and Phenylephrine*

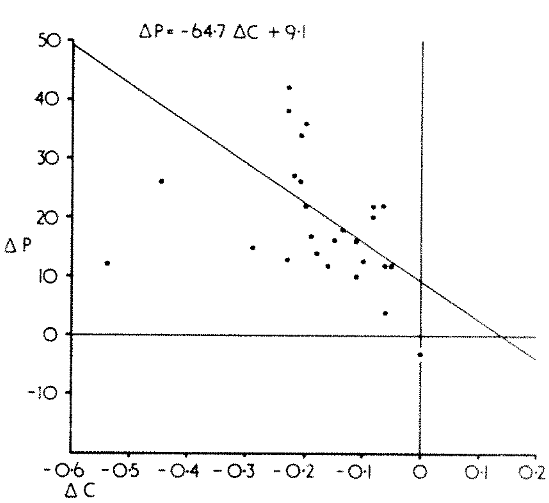

Fig. 4 *A plot of the total change in pressure (ΔP) against the total change in C (ΔC) in the 26 eyes. The equation of the regression line is ΔP = −67·4 ΔC + 9·1; the correlation coefficient is −0·6*

A plot of the total change in pressure (ΔP) against the total change in outflow (ΔC) is shown in Fig. 4. The equation of the regression line is ΔP = −67·4 ΔC + 9·1. The correlation coefficient is −0·6, that is, there is a highly significant negative linear correlation between these two variables (P < 0·001).

Discussion

Normal eyes respond to provocative testing with pilocarpine and phenylephrine by developing an increase in outflow (Mapstone, 1977). In the 26 eyes described here there was a very significant decrease in outflow at the end of the test. Since there is no reason to suppose that their outflow systems are in any way different from normal—apart from a high probability of developing angle closure—the most probable explanation of the reduction in C is angle closure. This conclusion is supported by the presence of a highly significant negative linear correlation between the changes in outflow and pressure.

The 26 eyes showed 3 separate patterns of response. The first (Fig. 1) would seem predictable—that is, approximately an hour after the start of the test the angle was closed by irido-corneal contact, and pressure increased by 20 mmHg. It is also apparent that the angle became closed as the pupil *moved up* to the position of mid-dilatation.

The 7 eyes exhibiting the second response (Fig. 2) increased C by 63% after the lapse of 1½ hours, and pressure decreased by an insignificant amount—that is, no portion of the angle closed as the pupil moved to mid-dilatation. The instillation of a second dose of pilocarpine and phenylephrine then produced an opposite response, with the angle occluding almost completely.

In the third response (Fig. 3) 80 minutes after the first dose of pilocarpine and phenylephrine C decreased by 55%, but pressure had increased by an insignificant amount. At the same time the pupil had moved to mid-dilatation. It is, of course, possible that after an appropriate period this group of eyes would have proceeded inexorably to an acute attack even if no further drugs were instilled. In the event an additional dose of pilocarpine and phenylephrine was instilled, and 74 minutes later the angle was almost completely occluded and pressure increased by 23 mmHg. This group of eyes therefore produced partial angle closure as th pupil moved to mid-dilatation but an insufficien pressure increase to produce a positive result. Th addition of pilocarpine and phenylephrine at mid dilatation then closed the angle.

The clinical implications of these varying pattern of response are explored in subsequent papers. It is however, apparent that a substantial proportion o the angle can close without the production of significant pressure change. The limiting factors ar the extent and duration of angle closure.

I am grateful to colleagues who referred patients fo study and to Mrs E. Tubb for secretarial help.

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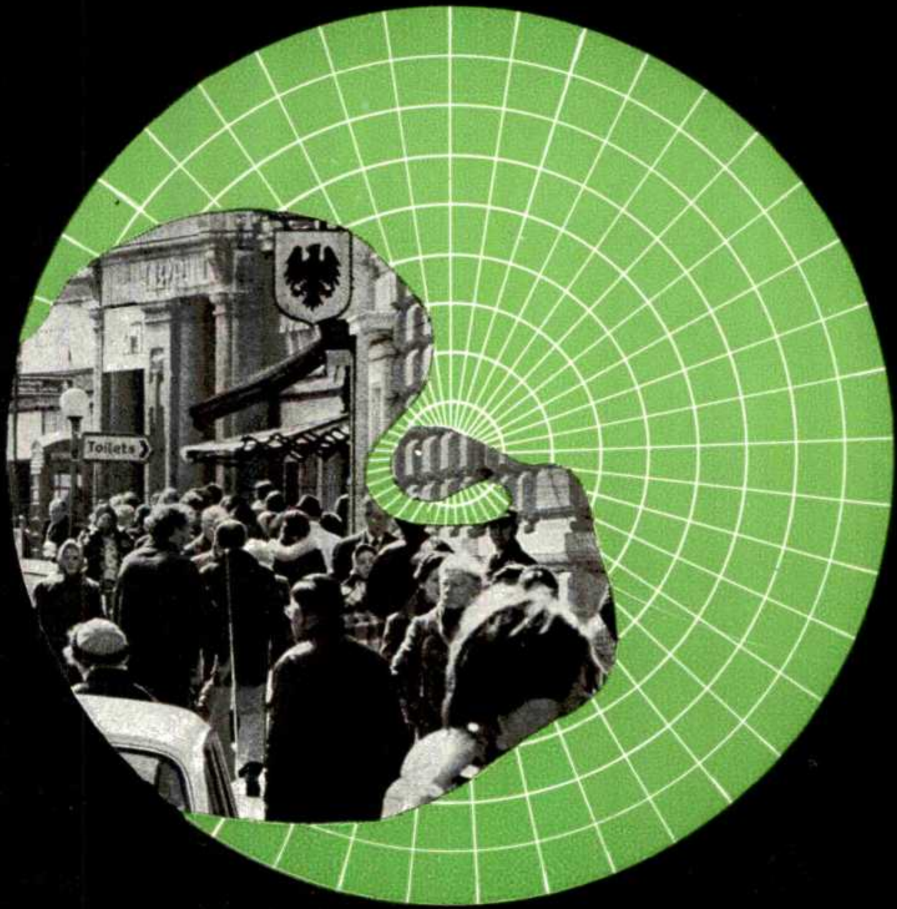

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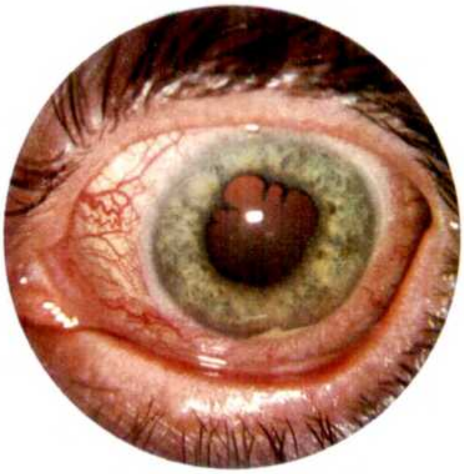

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Outflow changes in normal eyes after closed-angle glaucoma

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SUMMARY Twenty-four patients with spontaneous acute closed-angle glaucoma in one eye were selected for study. All 24 eyes had a peripheral iridectomy, were normotensive, and had no gonioscopically visible peripheral anterior synechiae. Of the 24 contralateral eyes 14 gave a positive response to provocative tests and had peripheral iridectomy. The remaining 10 eyes did not give positive responses to the tests and were on no treatment.

The 24 pairs of eyes were provoked with pilocarpine and phenylephrine. Tonography was performed at the start of the test, 1½ hours later, and at its termination. At the start of the test the 24 eyes that had had spontaneous closed-angle glaucoma showed a higher pressure and lower outflow facility than the 24 contralateral eyes. This difference disappeared as the test progressed. It was concluded that apparently normal eyes—after an acute attack—do none the less show a significant degree of damage to the outflow system. Ten pairs of eyes from 10 normal persons were provoked in a similar fashion and at no point did a significant difference appear between right and left eyes.

After an attack of spontaneous acute closed-angle glaucoma and subsequent iridectomy some eyes still need treatment. The cause of this residual increase in pressure is either permanent occlusion of part or all of the angle by peripheral anterior synechiae, or (it is postulated), if none are visible, damage to the trabecular meshwork.

If an acute rise in pressure can cause so much damage to the outflow system—in the absence of anterior synechiae—that pressure remains high, then it would seem reasonable to suppose that it could also produce an outflow deficit insufficient to require treatment. Therefore some eyes that are normotensive after iridectomy would have a reduced outflow facility. An investigation of that hypothesis is reported here.

Material and methods

Twenty-four patients were selected on the following criteria: (*a*) An attack of acute closed-angle glaucoma in one eye treated by a peripheral iridectomy. Subsequently, all eyes were normotensive on no treatment and had had no gonioscopically visible peripheral anterior synechiae. (*b*) The 24 contralateral eyes had no evidence of closed-angle glaucoma and were provoked with simultaneous pilocarpine and phenylephrine (Mapstone, 1976). If the test was positive a peripheral iridectomy was done (14 eyes), if negative no treatment was given (10 eyes).

The 24 patients were then provoked as follows: At zero hours intraocular pressures were recorded and tonography done on the right eye. Immediately afterwards tonography was done on the left eye. Pilocarpine 2% and phenylephrine 10% drops were then instilled into both eyes. Approximately 45 minutes later pressure was recorded and phenylephrine drops 10% were instilled. After the lapse of another 45 minutes pressures were recorded, tonography of right and left eyes was done, and pilocarpine 2% and phenylephrine 10% drops were instilled. One hour later, that is approximately 2½ hours after the start of the test, pressures were measured and tonography was repeated.

Ten patients with no evidence of glaucoma were provoked as described above.

The statistical tests used were paired *t* tests.

Results

PROVOCATIVE TESTS ON 24 PATIENTS

Fig. 1*a* records the result of provoking 24 eyes which had had an acute attack of closed-angle glaucoma. The first dose of pilocarpine and phenylephrine produced a significant fall in pressure, from a mean of

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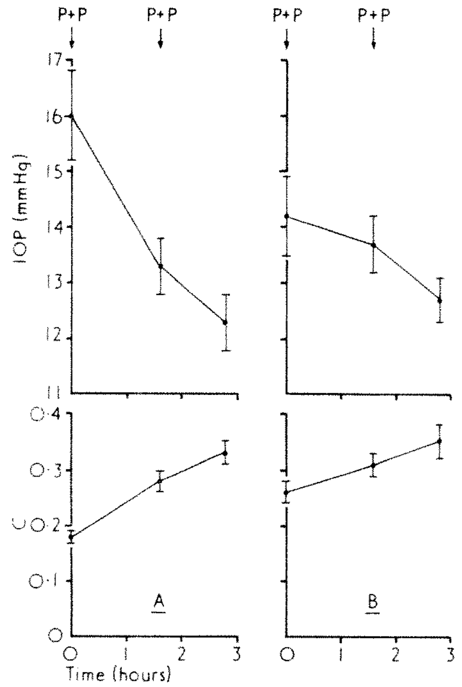

Fig. 1*a* *Response of 24 eyes that had had a spontaneous attack of closed-angle glaucoma and subsequent peripheral iridectomy to provocative testing with simultaneous pilocarpine and phenylephrine. Mean and standard error recorded. P and P = pilocarpine and phenylephrine*

Fig. 1*b* *Response of 24 contralateral eyes that had not had a spontaneous attack of closed-angle glaucoma to provocative testing with simultaneous pilocarpine and phenylephrine. Mean and standard error recorded*

16·0 mmHg to a mean of 13·3 mmHg ($P<0{\cdot}001$); and a significant increase in C, from a mean of 0·18 to a mean of 0·28 ($P<0{\cdot}001$). The second dose of pilocarpine and phenylephrine also produced a significant decrease in pressure ($P<0{\cdot}01$) and a significant increase in C ($P<0{\cdot}05$).

Fig. 1*b* records the results of provoking the 24 contralateral eyes that had not had a spontaneous attack of acute closed-angle glaucoma. The first dose of pilocarpine and phenylephrine produced an insignificant decrease in pressure from a mean of 14·2 to a mean of 13·7 mmHg, but a significant increase in C, from a mean of 0·26 to a mean of 0·31 ($P<0{\cdot}01$). The second dose of pilocarpine and phenylephrine produced a significant decrease in pressure ($P<0{\cdot}05$) and a significant increase in C ($P<0{\cdot}01$).

A comparison of Figs. 1*a* and 1*b* shows that before the test the eyes that had had a spontaneous acute attack had a significantly higher pressure ($P<0{\cdot}001$) and a significantly lower C ($P<0{\cdot}001$) than the contralateral normal eyes. At the time of instillation of the second dose of pilocarpine and phenylephrine there was no significant difference in pressure between the two groups of eyes, but C in the eyes with an acute attack was still significantly lower ($P<0{\cdot}05$). At the termination of the provocative test there was no significant difference between the two groups of eyes, in either pressure or outflow facility.

PROVOCATIVE TESTS ON 10 NORMAL PATIENTS
Fig. 2 records the result of provoking 10 normal patients with pilocarpine and phenylephrine. Both the decrease in pressure and increase in C in both eyes is significant ($P<0{\cdot}001$), but no significant difference appeared *between* right and left eyes at any stage during the test.

Discussion

The interpretation of provocative test results in eyes that have had a peripheral iridectomy requires care. Although at the start of the test the angles were open and free of synechiae, the first dose of pilocarpine and phenylephrine moves the pupil to mid-dilatation and might produce partial angle closure with a decrease in C and increase in pressure. There are reports that this can happen. For example, Lowe (1964) dilated pupils (that had previously had a peripheral iridectomy for closed-angle glaucoma) with parasympatholytic drugs and in 19% produced a

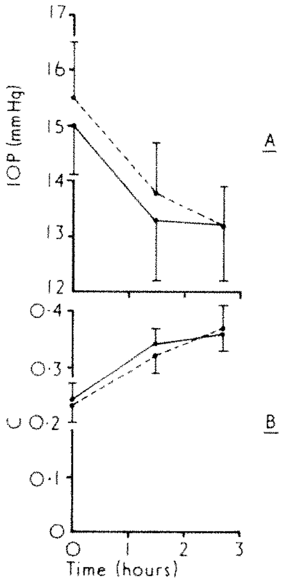

Fig. 2*a* *Pressure response of 10 pairs of normal eyes during a pilocarpine-phenylephrine provocative test. Mean and standard error recorded*
—— = right eyes
- - - - = Left eyes

Fig. 2*b* *Outflow response of 10 pairs of normal eyes during a pilocarpine-phenylephrine provocative test. Tonography done on right eye and immediately afterwards on the left eye. Mean and standard error recorded* significant increase in pressure. In a later rejoinder (Lowe, 1969) to a paper by Harris and Galin (1969) he states, 'high pressure rises occurred only when angles were totally occluded by iris folding.' In contrast Harris and Galin (1969) performed a similar investigation and produced a significant pressure rise in 21%. But the pressure increase occurred only in patients who had previously had a raised tension (Lowe's were all normotensive), and 'no angle was felt to be occluded at any time in this study'. They concluded that a decrease in ciliary muscle tone induced a reduction in outflow facility.

It has been shown (Mapstone, 1977) that the response of normal eyes to the simultaneous instillation of pilocarpine and phenylephrine is to develop a significant increase in outflow. Furthermore (Mapstone, 1977) 60% of contralateral eyes at risk to closed-angle glaucoma (which did not develop a positive provocative test) showed a significant reduction in outflow at some stage during the test which was probably due to partial angle closure. Of the 24 eyes described here that had a spontaneous acute attack 2 showed a reduction in outflow at some stage during the provocative test. In the 24 contralateral eyes 6 produced a similar result, 4 of which had not had peripheral iridectomies.

The 24 eyes with spontaneous closed-angle glaucoma had at the start of the test a significantly higher pressure and lower outflow than the 24 contralateral eyes. But the effect of pilocarpine and phenylephrine as the test progressed was to cancel this difference, so that at the end both groups of eyes had equivalent pressures and outflow.

The first question to be asked is what is the cause of the asymmetry, and there would seem to be five main possibilities. Firstly, it could be argued that the presence of previous open-angle glaucoma is the cause of the differences. This is almost certainly not so, since it would be necessary to postulate its presence in all 24 eyes, and unilaterally too. Secondly, the effect of a raised pressure on outflow resistance could be advanced in explanation. Ellingsen and Grant (1971a, b) have shown that outflow resistance is to some extent pressure-dependent—that is, the higher the pressure the lower is outflow—and Johnstone and Grant (1973) and Grierson and Lee (1974) have postulated a mechanism. In the 24 pairs of eyes, however, the pressure difference is small. It is therefore unlikely that this mechanism was of much significance. Thirdly, numerous authors have indicated a 'consensual' effect when tonography is done on both eyes consecutively. There seems to be no agreement as to the direction of the effect (i.e., whether an increase or decrease in C is produced in the contralateral eye). Provocative tests done on 10 normal patients indicate no significant difference between right and left eyes. This mechanism therefore would appear not to be contributory. Fourthly, it is possible that partial-angle closure might explain some of the observed discrepancy. Again this is unlikely, since the angles were open at the start of the test, and, as mentioned above, reductions in C were not very common.

The final possibility is that an acute rise in intraocular pressure produced damage to the outflow pathways which significantly reduced C and increased pressure relative to the contralateral eye. These changes were reversed by the provocative test.

The nature of the damage to the outflow system is of interest. Grant and Trotter (1955) and Becker and Constant (1956) have shown that outflow values are similar in eyes *in vivo* and when perfused post mortem. Metabolic inhibitors and wide variations in temperature (Van Buskirk and Grant, 1974) also have little influence on outflow in excised eyes. Finally, Van Buskirk and Grant (1973) showed that mechanical traction (lens depression) on angle structures increases outflow. If, therefore, outflow changes are determined largely by mechanical factors, it would seem that an acute rise in pressure induces a mechanical change that is completely reversible by a mechanical process (Bárány, 1966).

Whatever may be the explanation, it is apparent that eyes judged to be clinically normal after an attack of closed-angle glaucoma do none the less show a significant reduction in outflow and increase in pressure relative to the contralateral eye. To say that this is a secondary change—which it is—but therefore because of this not comparable to the change in open-angle glaucoma, begs the question, since it assumes that the reduction in outflow in open-angle glaucoma is in some way primary (although it must have a cause). Open-angle glaucoma is 'primary' only because the causal mechanism(s) is unknown. Again, there is no reason to suppose that there must be one unique 'cause' for reduced C values in open-angle glaucoma, and these results raise the possibility that one such cause may be an increase in pressure produced by an angle-closing mechanism.

I thank Mrs E. Tubb for secretarial help.

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British Journal of Ophthalmology, 1977, **61**, 641–645

Circulating lipoprotein and blood glucose levels in association with low-tension and chronic simple glaucoma

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SUMMARY Circulating lipoprotein and blood glucose levels were determined for 53 patients with low-tension glaucoma and 39 patients with chronic simple glaucoma. The incidence of hypercholesterolaemia was significantly higher in the low-tension group than in the chronic simple glaucoma group and control data obtained elsewhere. Preliminary follow-up results of the effects of treatment are also reported. The incidence of raised fasting blood glucose levels was not significantly increased in either group.

It is widely held that vascular influences are important in the development of disorders of intraocular pressure and particularly of low-tension glaucoma (Drance, 1975). These influences may include lipoproteinaemias. Miller (1972) noted that raised serum cholesterol values were common in patients with low-tension glaucoma, and Winder *et al.* (1974) reported that the incidence of lipoproteinaemias, and particularly the type IIA disorder, was raised in patients with ocular hypertension and low-tension glaucoma but not apparently in a small group of patients with chronic simple glaucoma. Walker *et al.* (1976) found that hyperlipoproteinaemias were common in patients with ocular hypertension and chronic simple glaucoma and in a small group of patients with low-tension glaucoma, but they concluded from control studies that the incidence in these disorders was not exceptional for the age groups involved, a conclusion supported by a further small study of low-tension glaucoma by Joist *et al.* (1976).

Further studies on this association are now reported, and since fasting samples were necessary the opportunity to record fasting blood glucose levels in these disorders was also taken.

Methods

DIAGNOSTIC CRITERIA

The criteria employed by the clinical units forwarding patients and/or samples for this study were unchanged from those of the previous report (Winder *et al.*, 1974), that is:

Low-tension glaucoma. An intraocular pressure of 21 mmHg or below in a patient having open angles, pathological cupping of the optic disc, and a glaucomatous field defect. This group includes a few monocular cases with tensions in both eyes below 21 mmHg.

Chronic simple glaucoma. An intraocular pressure of 22 mmHg or above in a patient having open angles, pathological cupping of the optic disc, and a glaucomatous field defect.

All pressures were recorded with the Goldmann applanation tonometer.

PATIENTS

Low-tension glaucoma. Studies were performed on 53 patients—21 males of average age 63·4 years, 32 females of average age 55 years (Fig. 1).

Chronic simple glaucoma. Studies were performed on 39 patients—20 males of average age 59·6 years, 19 females of average age 61·8 years (Fig. 2).

Patients and/or samples were considered on a first-come first-served basis, and no selection bias was apparent. No patient was a known diabetic prior to laboratory examinations in this study.

ANALYTICAL METHODS

Plasma lipid and lipoprotein analyses were performed on samples collected into EDTA anticoagulant containers after an overnight fast of at least 12 hours. Cholesterol and triglycerides were determined by standard automated colorimetric and semiautomated fluorimetric procedures respectively,

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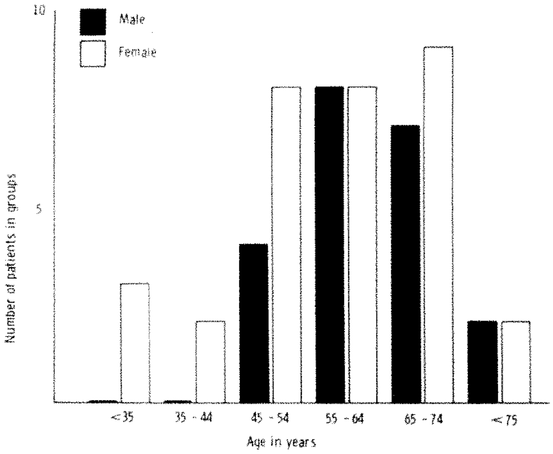

Fig. 1 *Low-tension glaucoma: age distribution of 53 patients*

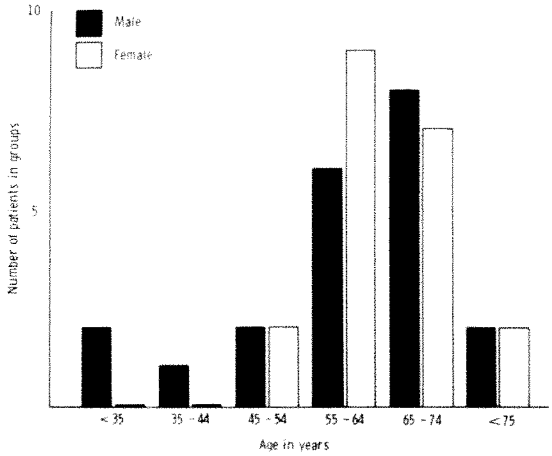

Fig. 2 *Chronic simple glaucoma: age distribution of 39 patients*

and lipoprotein patterns were defined by inspection after electrophoresis on Cellogel and classified in accordance with current WHO nomenclature. Secondary hyperlipoproteinaemia was considered when specific causes—for example, alcoholism—arose, but no defined secondary disorder was found in this series of patients.

Glucose tolerance tests were performed and evaluated in the standard manner (Fitzgerald and Keen, 1964) using a Lucozade test load, and blood glucose levels were determined by an automated version of the glucose oxidase method.

All these analytical methods were subject to continuous quality control procedures.

Results

LOW-TENSION GLAUCOMA

Fasting blood glucose. Forty-four values were recorded, including 7 forming part of a glucose tolerance test. One woman aged 58 years showed mild elevation of fasting blood glucose, and 2 men aged 70 and 73 years showed adequate fasting control but impaired tolerance.

Lipoprotein. Fasting lipid/lipoprotein profiles were recorded for 51 patients and non-fasting (normal-range) values were obtained for two further male patients. Fasting triglyceride levels were mildly elevated in two patients, in one case in a type IIB pattern with cholesterol elevation. Values for cholesterol are shown in Fig. 3. One woman aged 54 years gave a normal-range fasting profile, but an elevated non-fasting cholesterol value had by chance been recorded a few weeks before the test, indicating reduced lipid tolerance. This value is marked with an arrow in Fig. 3.

CHRONIC SIMPLE GLAUCOMA

Fasting blood glucose. Thirty-two values were recorded, including 4 forming part of a glucose tolerance test. One man aged 71 years showed marked elevation of fasting blood glucose, and 1 woman aged 56 years showed adequate fasting control but impaired tolerance.

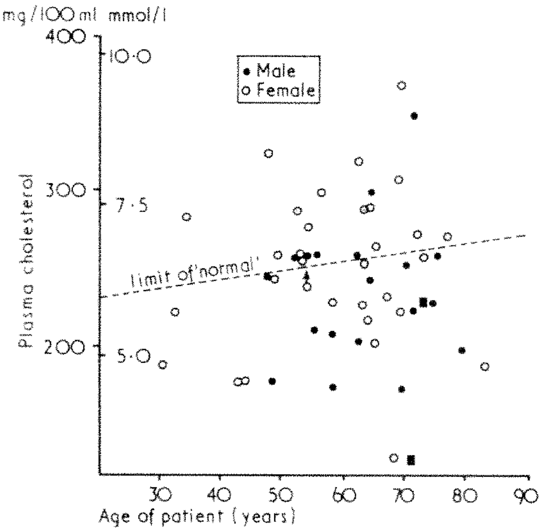

Fig. 3 *Plasma cholesterol values in 53 patients with low-tension glaucoma, by age and sex. The squares indicate two non-fasting values; all others are fasting, including one value with arrow attached for a patient with impaired lipid tolerance. A proposed normal limit is also shown*

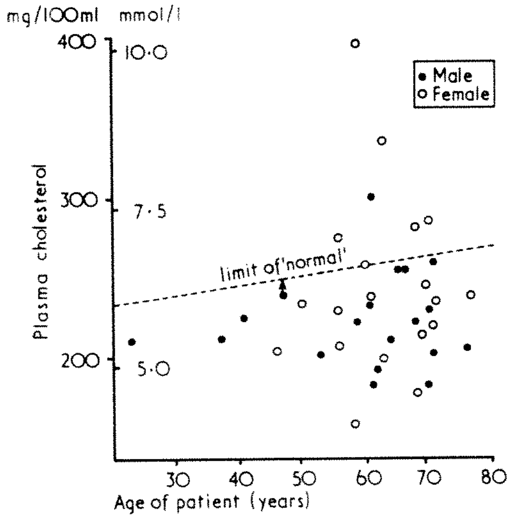

Fig. 4 *Fasting plasma cholesterol values in 39 patients with chronic simple glaucoma, by age and sex. The fasting value for a patient with impaired lipid tolerance is shown with arrow attached. A proposed normal limit is also shown*

Lipoprotein. Fasting lipid/lipoprotein profiles were recorded for all 39 patients. Triglyceride levels were moderately elevated in 1 woman aged 58 years in a type IV pattern and mildly elevated in 2 further men. Values for cholesterol are shown in Fig. 4, where a male aged 47 years with fasting control but impaired lipid tolerance is also indicated.

ASSESSMENT

Fasting blood glucose. The incidence of abnormality does not exceed that found with normal subjects in this age distribution.

Circulating lipoprotein. Markedly elevated lipoprotein levels were not a feature of the 2 forms of glaucoma considered, and the incidence of hypertriglyceridaemia was not excessive for either group, but the cholesterol/β-lipoprotein levels were generally on the high side for the low-tension group and not obviously different from normal for the chronic simple glaucoma group. In the absence of an appropriate control study these results were assessed by reference to surveys performed on a healthy population in the London area (Lewis *et al.* 1974) and by intergroup comparison.

Reference to a 'normal' population

Lewis *et al.* (1974) established percentile ranges for fasting serum cholesterol separately for males and females in the age groups 20 to 39 and 40 to 69 years. These data and those shown in Fig 3 for low-tension glaucoma show the results for 1 of 3 women in the 20 to 39 age group, and 4 of 24 women and 1 of 13 men in the 40 to 69 age group, exceed the 95th percentile, while results for a further 2 women in this latter group exceed the 90th percentile, giving overall values of 6 of 39 results beyond the 95th percentile and 8 of 39 beyond the 90th percentile. A chi-squared test shows these differences are significant at the level of $P<0{\cdot}05$ for the overall group at the 95th percentile and for females in the 40 to 69 age group at the 90th and 95th percentiles. In this study several male patients with low-tension glaucoma fell in the 70+ age group not considered in the above comparison, and the emphasis on female patients is not necessarily significant. For the chronic simple glaucoma group with results shown in Fig. 4, 3 of 30 values in the 40 to 69 age group exceeded the 95th percentile, and no aspect of this distribution was significantly different from normal.

Comparison between the two categories of glaucoma

Assessment in our previous study (Winder *et al.*, 1974) was based on an age-weighted upper limit of normal for fasting plasma cholesterol from 240 mg% at 30 years of age to 260 mg% at 65 years, derived essentially from the remarks of Lewis (1972). This limit is shown in Fig. 3 and 4, and is exceeded by 22 of 53 (41·5%) results for low-tension glaucoma and equalled or exceeded by 7 of 39 (18%) results for chronic simple glaucoma. A chi-squared test shows this difference is significant at the level of $P<0{\cdot}02$. A further limit was drawn 20 mg% higher and the intergroup difference was not then significant, which supports the impression that the difference was dependent on relative rather than gross hypercholesterolaemia.

Discussion

The significance of any relationship between low-tension glaucoma and hyperlipoproteinaemia, particularly of the type IIA pattern, depends less on the absolute incidence than on the comparison with that in the normal population, and this aspect creates real difficulties for a specialist eye hospital. Control data were previously obtained by reference to a uveitis clinic (Winder *et al.*, 1974) but for the present study control data obtained elsewhere for a 'normal' population in the same general catchment area were drawn upon (Lewis *et al.*, 1974).

Walker *et al.* (1976) described similar problems with their survey in the Birmingham area, and they fell back on control data obtained for a large group of healthy individuals and patients attending a general hospital, for which, however, some difficulties still arise. Walker *et al.* found that the incidence of hyperlipoproteinaemia in association with low-tension glaucoma and other disorders of intraocular pressure was high but not different from the incidence in the control group, but the normal limits were constructed on a percentile basis with a continuously age-weighted increase, and many of the control hospital data applied to non-ambulant patients on hospital (i.e., changed) diets, giving serum lipid/lipoprotein values rather higher than those found in the local population at large (Magnani, 1977, personal communication). The study included 10 male and 3 female patients with low-tension glaucoma, and fasting cholesterol values were high in the females of this group, significantly more so than the males. This sex difference was also seen in the larger chronic simple glaucoma group.

Drance *et al.* (1973) assessed various factors, including serum lipoproteins, which might have a bearing on blood coagulation in a group of patients with low-tension glaucoma, using a further group of patients with ocular hypertension as controls. A surprisingly high incidence of known diabetes was recorded for the low-tension glaucoma group, but although an increased incidence of hypercoagulable states was recorded the incidence of hyperlipoproteinaemia did not exceed that found in the control group. This comparison may be inappropriate, as ocular hypertension can also be associated with an creased incidence of hyperlipoproteinaemia (Winder *et al.*, 1974). In a further small group study Joist *et al.* (1976) were unable to confirm that hypercoagulable states, including hyperlipoproteinaemias, were involved in the pathogenesis of low tension glaucoma. Individually matched normal subjects were used as controls in this study, and this form of comparison is more secure when large groups are involved, particularly when the differences under consideration are not absolute. Finally, the age-weighted control limit used in the present study for the low-tension/chronic simple glaucoma intergroup comparison is not unduly conservative in view of the known associations between serum cholesterol, age, and the risk of ischaemic heart disease (Editorial, 1977).

Differences in methodology, precision, and quality control may apply to all these studies. Walker *et al.* (1976) were particularly careful here using multiple lipid determinations at 3 centres, and results in the present study were backed up by agreement with the patterns obtained by lipoprotein electrophoresis; some variations in clinical definitions and patient classification are also found. The association between low-tension glaucoma and hyperlipoproteinaemia of the type IIA pattern reported in the present study is derived from the largest group of patients and data collection so far considered. The relationship has developed continuously over a 4-year period of study, and the differences emerging between this and the parallel study on chronic simple glaucoma proceeding over the same period strongly suggest that bias in the methodology is not involved. The provision of control data has been a problem in all the studies cited, and various compromise approaches have been attempted. Hopefully the development of cause-and-effect hypotheses will allow patients to function as their own controls as the effect of the appropriate treatment on the clinical defect is monitored.

A range of vascular and haemodynamic influences have now been reported for low-tension glaucoma, which have in general not been confirmed by follow-up studies at other centres. This confusion may in part reflect the operation of a multiplicity of factors, none distinctive, in a condition with a substantially heterogeneous pathogenesis (Drance, 1975). The lipoprotein elevation shown for low-tension glaucoma was not gross and was in any event not shown by the majority of the patients studied. This influence was not obvious for chronic simple glaucoma. There is certainly no simple general relationship between the 2 forms of glaucoma, which perhaps again reflects the operation of a mixed, variable and presumably overlapping pathogenesis.

Various cause-and-effect relationships were considered when the possible relationship between hyperlipoproteinaemias and this group of ocular disorders became apparent (Winder *et al.*, 1974). An influence on blood viscosity, particularly at the low shear rates operating in smaller vessels (Newman and Twinn, 1973), seemed particularly attractive. This might affect perfusion at the optic nerve head and/or lead to restriction of drainage back into the circulation from the aqueous veins. Short-term reductions in the level of plasma cholesterol and blood viscosity can readily be produced in hyperlipidaemic patients by dietary change, and follow-up studies on such patients, including some with low-tension glaucoma, together with the observations of Gloster (1974) on the responses to clofibrate (Atromid) in ocular hypertension and chronic simple glaucoma, have not revealed an immediate clinical response, which reduces the likelihood that blood viscosity is an important primary immediate influence. Degenerative processes and atherosclerosis may be involved, presumably on a selective basis, and observations on the response of xanthomata in hypercholesterolaemic subjects to dietary restriction indicate that some years may elapse before positive clinical and biochemical responses are obtained (Palmer and Blacket, 1972). Lipoproteinaemias are also commonly secondary disorders (Chait, 1972), and the primary metabolic disorders involved may be the pertinent influences on the ocular condition.

Long-term follow-up studies in association with dietary and therapeutic control are required and are to a limited extent proceeding in conjunction with the general practitioners involved, but logistic problems do arise because of the lack of short-term response, and therefore poor motivation of patient and family, and because of the necessity for prolonged maintenance of control. Patients in whom the association arises cannot be offered the prospect of early clinical improvement or even any improvement at all on present evidence, but the association is sufficiently evident to justify lipoprotein screening in low-tension glaucoma, and at least the general benefits of control where necessary are increasingly well supported.

I am grateful to Professor J. Gloster, Mr B. Cobb, Mr R. Hitchings, Mr R. J. H. Smith, Mr S. J. H. Miller, and Dr G. Paterson for referral of cases and advice at various times, to the Frost Trust for generous financial support, and to the many patients who have taken part in this study.

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The influence of pregnancy on the sensitivity of the cornea

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SUMMARY Corneal touch thresholds (CTT) were measured in 30 non-pregnant women serving as a control group and 29 pregnant women at different times during and after pregnancy. The results show that CTT becomes significantly higher after 31 weeks of pregnancy. However, only 86% of the subjects showed a difference in CTT during and after pregnancy, while 52% reported having some swelling. The loss of sensitivity (CTT^{-1}) is assumed to be related to the water retention occurring during pregnancy, a view which is supported by some measurements of corneal thickness. It is suggested that this study may have exposed a new, hitherto unknown, way of monitoring pregnant women.

Corneal sensitivity has been shown by Millodot and Lamont (1974) to decrease during the premenstrual phase of the woman's menstrual cycle. Many of the changes occurring during the premenstrual phase are similar to those of pregnancy (Best and Taylor, 1945). Hence it was felt that corneal sensitivity may also be affected in pregnant women, especially when hydration is manifest, since it is known that corneal oedema gives rise to a loss of corneal sensitivity (Millodot, 1975a). The purpose of this study is to report changes in corneal sensitivity taking place in many normal pregnant women.

Material and methods

The Cochet-Bonnet aesthesiometer (Cochet and Bonnet, 1960) based on the instrument devised by Boberg-Ans (1955) was used to stimulate the cornea. The instrument consists of a nylon monofilament of 0·12 mm diameter which can produce pressures ranging from 11 to 200 mg/0·0113 mm². The aesthesiometer was mounted in a holder so that it could be moved in x, y, and z planes by means of three knobs. Thus, it was possible to achieve reliability in stimulation of the same corneal point, a steady speed of application, and a perpendicular corneal contact. A corneal point near the lower limbus was stimulated, and the slightest bend of the nylon wire was defined as corneal contact while the subject fixated a target in front and above her. The peripheral corneal point was chosen because the touch threshold measured there is usually unaffected by apprehension factors (Bonnet and Millodot, 1965).

Measurements of corneal touch threshold (CTT) were made subjectively (Millodot, 1973). The experiment began with the lowest pressure and continued in an ascending fashion. At each predetermined length of the monofilament (with increments equal to 0·5 cm) 4 to 6 contacts were made with at least one blank to test the subject's reliability. The subject indicated when she felt the probe by operating a bell. From these measurements CTT was defined as the length of the monofilament at which the subject responded for 50% of the number of stimulations. This length was converted into pressure by means of a previously calibrated curve for the instrument. All measurements were taken when the humidity in the room ranged between 50 and 60% because the nylon monofilament is affected by humidity.

Twenty-nine normal pregnant women between 22 and 39 years old (mean 28·2; SD 3·6) participated in this investigation in response to an advertisement. All were in good health, and it is thought that none of them came from a low socioeconomic background. Each subject was asked whether she had noted any swelling, particularly of the ankles and fingers. All were tested at least once but many of them several times during pregnancy (1 of them every month from the third month onwards). CTT was measured again between 6 and 8 weeks after delivery. Care was taken to ensure that these measurements were carried out at about the same time of day with each individual to avoid confound-

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ing the results with the diurnal variation of corneal sensitivity (Millodot, 1972).

In addition a control group of 30 non-pregnant women aged between 21 and 40 were tested once in the same conditions as the pregnant women.

Results

The measurements obtained with the control group are shown in Fig. 1. The spread of the results confirms earlier measurements (Millodot, 1973). It is attributable to inherent biological differences and differences in eye colour (Millodot, 1975b).

The results for the pregnant women are also given in Fig. 1 as well as after delivery. The figure illustrates the fact that most pregnant women tended to have a higher CTT (that is a lower sensitivity) with advancing pregnancy, especially in the final phase. However, the difference in CTT between the control group of non-pregnant women and the pregnant women becomes statistically significant only in the 31 to 40 weeks range ($t = 2{\cdot}93$, $P < 0{\cdot}01$).

It is worth pointing out that only 25 of the 29 (86%) pregnant women showed a difference in CTT (> 10%) at some stage during pregnancy as compared to after delivery. Interestingly, those who had the greater increase in CTT appeared to be overweight for their height, a fact which corroborates other observations (Thomson *et al.*, 1967). Of these 25 subjects 15 reported slight swelling of either their ankles or fingers or both. In other words 15 of the 29 pregnant women (52%) had some symptoms. It must be noted that all these subjects were seen at odd times during pregnancy; had they been tested throughout gestation this last figure might have been greater. As a corollary the figure 86% might also have been higher. All 4 women who had no difference in CTT reported having had no swelling either.

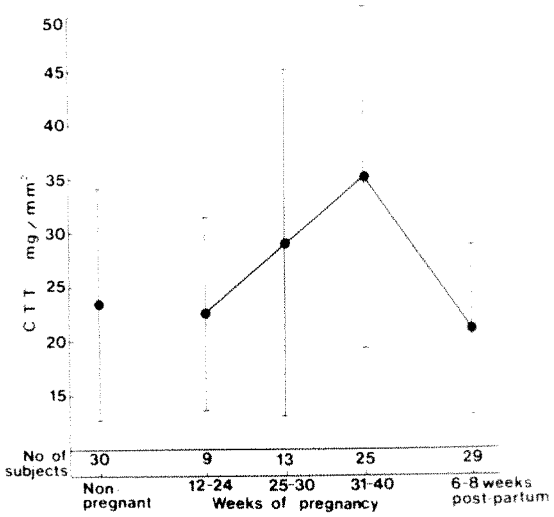

Fig. 1 *Mean corneal touch threshold (CTT) in a control group of non-pregnant women and in pregnant women during pregnancy and after delivery. The vertical lines represent ± 1 standard deviation*

Six to eight weeks post-partum CTT had returned to normal in all subjects and there was no significant difference between this group and the control group of non-pregnant women ($t = 1{\cdot}8$, $P > 0{\cdot}1$).

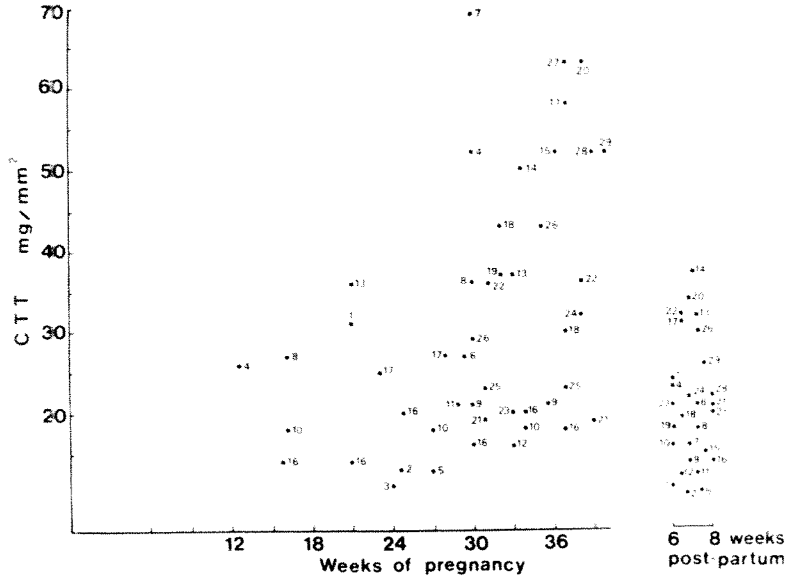

Fig. 2 *Individual measurements of corneal touch threshold during and after pregnancy. Each subject is indicated by the number placed next to each data point*

CORNEAL THICKNESS

Since there seems to be a relationship between the loss of corneal sensitivity and swelling in pregnancy, it was thought that the cornea may also become oedematous. It has already been shown that corneal oedema accompanies the changes occurring in corneal sensitivity as a result of contact lens wear (Millodot, 1975a). Thus corneal thickness, which is an index of corneal oedema (Mishima and Hedbys, 1968), was measured in 5 pregnant women when their CTT was appreciably above normal. Measurements of central corneal thickness were made with a Haag-Streit slit-lamp 900 and pachometer. The results are given in Table 1. They provide some evidence of corneal oedema in pregnant women, though it is quite slight. Moreover, the amount of corneal oedema appears to be unrelated to the severity of corneal sensitivity loss.

Discussion

The decline in corneal sensitivity demonstrated in this study parallels the increasing weight and water retention known to occur in pregnancy (Hytten and Leitch, 1971). The fact that some increase in corneal thickness was found supports the view that the cornea also was oedematous. But the slight increase in corneal thickness, uncorrelated to the loss of corneal sensitivity, may indicate that the reduction in the sensitivity of pregnant women's corneas may involve some other changes taking place at a higher level. However, the greatest losses of corneal sensitivity were usually found in women who reported swelling of their ankles or fingers or both.

The fact that only 52% of the pregnant women reported some swelling (mostly slight) seems somewhat low as compared to the observations of Robertson (1971). He found that 83% of pregnant women, whom he tested throughout pregnancy, reported swelling at some stage. But, as noted earlier, the low figure obtained here may be explicable by the fact that the pregnant women were seen only at odd times during gestation. It is interesting, though, that by testing corneal sensitivity 86% of the pregnant women showed a difference from their sensitivity after delivery. And since loss of corneal sensitivity always accompanies corneal oedema, however slight (Millodot, 1975a), the results of this study may be regarded as providing evidence supporting Robertson's claim (1971) that increased hydration may be universal in normal pregnancy.

Table 1 *CTT (mg/mm^2) and corneal thickness (mm) measured in 5 pregnant women at some time (weeks) during pregnancy and 6 to 8 weeks after delivery*

		During pregnancy			*After delivery*	
Case No.	*Time*	*CTT*	*Corneal thickness*	*Symptoms*	*CTT*	*Corneal thickness*
17	37	58	0·58	Fingers swollen	31	0·53
22	36	36	0·57	None	32	0·54
27	37	63	0·60	Ankles and fingers swollen	16	0·56
28	39	52	0·57	Ankles swollen	21	0·53
29	40	52	0·58	Fingers swollen	24	0·53

The increase in corneal touch threshold in pregnant women has apparently never been reported before. It offers an alternative means of monitoring the progress of pregnancy. Moreover, it is quantifiable and may be an early detector, since a much higher percentage of pregnant women was thus detected than by asking the patient. And in all cases but one high CTTs were accompanied by a report of swelling. The monitoring of pregnancy by this method could be useful in preventive therapy.

The loss of corneal sensitivity during pregnancy cannot account for the difficulty encountered by some women in wearing their contact lenses. It is more likely to be due to a variation in corneal topography as a result of oedema. An alteration of the composition of the tears may also occur, as these patients often complain that their lenses become greasy soon after they have been inserted in the eyes. Indeed, lysosyme, which is a viscous component of the tears, is secreted in greater quantity when there is generalised oedema (Moses, 1970).

Since a change in the topography will alter the power of the eye, and since corneal oedema leads to a change in corneal index (Fatt and Harris, 1973), it is not advisable to prescribe a new optical correction until some weeks after delivery.

Finally, it should be noted that a slight decrease in intraocular pressure (IOP) has been observed during pregnancy (Marx, 1923; Hørven and Gjønnaess, 1974). Although it is known that there is a reduction in corneal sensitivity with an increase in IOP (Boberg-Ans, 1955), it is not known whether a decrease in IOP would induce the same effect. The present results suggest that a fine balance in IOP may be needed for corneal sensitivity to remain unaltered.

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Corneal sensation in scleritis and episcleritis

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SUMMARY A series of 59 patients were examined for loss of corneal sensitivity. Thirty-five of them suffered from scleritis and 24 suffered from episcleritis. There was a difference between the 2 conditions in that significantly more patients with scleritis were affected than patients with episcleritis. It was also found that among the scleritis patients there was a close relationship between the number of quadrants affected and decrease in sensitivity. Five patients had necrotising scleritis, and they all showed marked loss of sensitivity. Sensitivity returned to normal when the scleritis resolved except when a large area of scleral ectasia resulted.

The test is of importance because it is one of the easiest methods of detecting the onset of necrotising scleritis in its earliest stages.

Episcleritis is a benign disease, causing no permanent damage to the eye and requiring only local therapy to hasten its resolution. Scleritis is a disease which, although varying greatly in severity, can be blinding on occasion. It requires systemic therapy and careful supervision in order to avoid the diastrous complications which may supervene.

It can be difficult at times to distinguish between the two conditions, especially when they are seen in the early stages, and it is at this stage that it is desirable to diagnose scleritis so that early treatment can be instituted. The presence of pain as opposed to discomfort, the vascular pattern, the appearance of scleral transparency, and the response to treatment are all of help when assessing a patient (Watson and Hazleman, 1976). Any additional clinical test that would be of value in distinguishing between episcleritis and scleritis would therefore be welcome.

It was thought that corneal sensation might be affected differently in the two conditions. Scleritis is usually a granulomatous condition destroying the sclera where the collagen fibres are more closely arranged, while episcleritis is an inflammatory condition in vascular tissues where collagen fibres of the episclera are more loosely arranged. The majority of nerve fibres subserving corneal sensation pass forwards between the sclera and choroid until they branch and pass through the sclera to the region of the limbus to form the perilimbal plexus. It would seem likely that scleritis would be more likely to cause swelling of the scleral fibres and consequent compression and possible destruction of the nerve fibres than would episcleritis. It is also known that corneal sensation may be profoundly affected in cases of sclerokeratitis due to herpes zoster, although other factors are operative here (Marsh, 1973).

In order to investigate the possible decrease in sensation in the two disorders a total of 59 patients attending the Scleritis Clinic at Moorfields Eye Hospital, City Road, London, suffering from scleritis and episcleritis were examined.

Methods

The instrument used to examine the corneal sensation was the corneal aesthesiometer of Cochet and Bonnet (Fig. 1). This instrument is based on the principle first described by von Frey and modified later by Boberg-Ans (Boberg-Ans, 1955). The instrument has many disadvantages but it does have the virtue of extreme portability and ease of manipulation. It consists of a filament of nylon contained in a holder, one end of the filament projecting out. The length of the projecting portion can be controlled by a small milled wheel on the handle. The instrument works on the principle that the longer the length of filament projecting, the less the pressure required to bend it.

The patient was placed in a reclining chair and was instructed to look at a point on the ceiling. The instrument was set on its longest length, which is 6 cm, and was slowly brought down to the corneal surface, ensuring that it was applied at right-angles to the cornea. The filament was pressed

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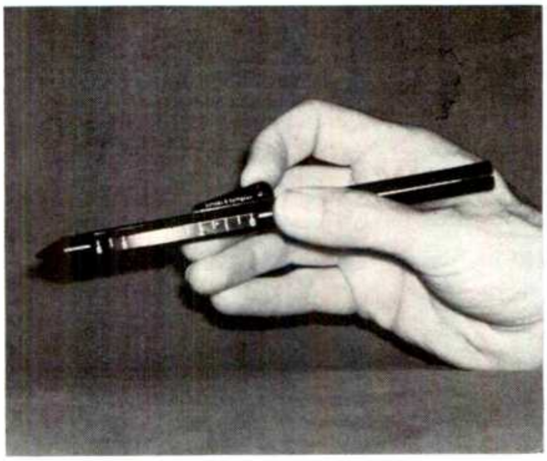

Fig. 1 *The corneal aesthesiometer of Cochet and Bonnet*

on the cornea until it could be seen to bend and the patient was asked to say if he felt anything. If he did, the filament length was recorded as 6 cm and the test repeated. Three tests on each of the points of the cornea to be described were performed on each occasion, and the result was recorded as positive if 2 out of the 3 were felt. If the patient felt nothing the filament was shortened by 1 cm and the test repeated. The filament was shortened by a centimetre progressively until the stimulus was felt, and the length of filament was then recorded in centimetres.

The corneal sensation at the centre of the cornea and in the 4 quadrants was tested as shown (Fig. 2).

The results of the test on each eye were recorded on a chart as shown (Fig. 3). It will be seen that, the lower the number of figures obtained in each region, the less acute the corneal sensitivity. Conversely, the higher the recorded number the greater the sensitivity.

The quadrants chosen were the temporal, nasal, superior, and inferior rather than superotemporal, inferotemporal, superonasal, and inferonasal, because it was felt that the nasal and temporal situation of the long ciliary nerves might be relevant. In fact it is doubtful if there would have been any difference in the findings.

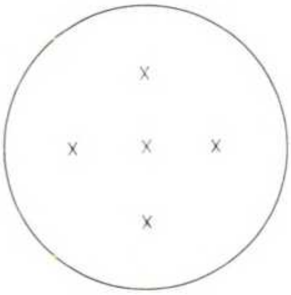

Fig. 2 *The positions on the cornea where sensitivity was measured*

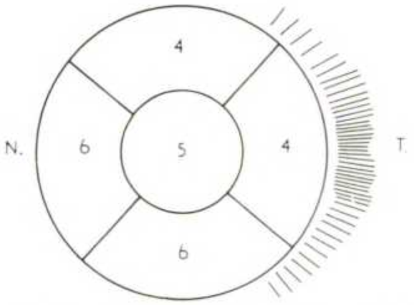

Fig. 3 *The charting of corneal sensitivities, with an area of inflammation recorded on the temporal side*

On the same chart the distribution of the scleritis was recorded by radial lines. The closer the lines were together the greater the intensity of the inflammation. A special note was made of areas of necrotising scleritis if present because it was felt that the latter was of particular importance. Cornea involved by sclerosing keratitis was indicated and staphylomata were also recorded.

In this investigation the corneal sensation of one eye was compared with the other so that factors such as humidity, which affects the elasticity of the nylon filament, diurnal variation of sensitivity (Millodot, 1972), menstruation (Millodot and Lamont, 1974), and age (Boberg-Ans, 1956) did not have to be considered. Testing in this way had the disadvantage that bilateral cases of scleritis and episcleritis could not be included in the trial.

In order to get consistent results with the instrument testing must be done with care, and particular attention must be paid to the following points: *(a)* The instrument must be applied at right-angles to the cornea. If this is not done the end of the filament skids across the corneal surface and variable answers are given by the patient. *(b)* Likewise, the instument must be held steady. If it is not the tip of the filament describes an ellipse on the cornea, which increases the stimulus. It is easy to keep the filament steady when it is short but by no means so when it is at its maximum length. *(c)* The lashes must not be touched by the tip or a positive response is immediately given. *(d)* The filament must approach the point to be tested from the side, otherwise it is seen by the patient and he gives a positive response almost before it touches the eye. *(e)* The filament must be applied slowly and steadily. *(f)* It is important that the stimulus is applied exactly half way between the centre of the cornea and the limbus in the 4 quadrants. Corneal sensation is normally most acute in the centre of the cornea and falls off rapidly as the limbus is approached. If the stimulus were to be applied at differing distances from the centre of the cornea widely different results would be obtained.

Results

A total of 59 patients were examined, 35 suffering from scleritis and 24 from episcleritis. The preponderance of patients with scleritis does not reflect the incidence of these conditions in the population but rather the fact that episcleritis tends to be treated successfully by the general practitioner and casualty department whereas the scleritis patients end up in a special clinic.

The results were charted by adding the numbers obtained in each quadrant of each eye together and then comparing the total for 1 eye with the other. It was thought that only a significant difference between the 2 eyes should be recorded as positive if the investigation was to be of value. The results obtained are subjective on the part of the patient, and patients vary greatly in their ability to give consistent responses. A difference of 3 or more was taken arbitrarily as being significant.

Out of the 35 patients suffering from scleritis 21 showed a decrease in corneal sensation. Out of the 24 patients suffering from episcleritis only 5 showed decreased sensitivity (Fig. 4). There is a significant difference in corneal sensation between the two conditions ($P < 0.05$).

When the patients with scleritis were analysed in more detail other interesting findings were revealed. It was found that the amount of perilimbal circumference involved was a significant factor. It seemed that a certain proportion of the perilimbal area needed to be affected before any effect upon sensation occurred. Many of these patients were examined during and after each recurrence in order to record recovery or otherwise of their corneal sensitivity.

The area of sclera involved was charted by means of the simple diagram already described and the number of quadrants involved recorded. It was found that those patients in which more than 1 quadrant was involved showed a greater incidence of decreased sensation than those in whom only 1 quadrant was involved. There were 27 episodes involving 1 quadrant and 13 of these showed decreased sensitivity, as compared with 15 episodes involving more than 1 quadrant in which 12 showed decreased sensitivity (Fig. 5) (statistically significant, $P < 0.05$).

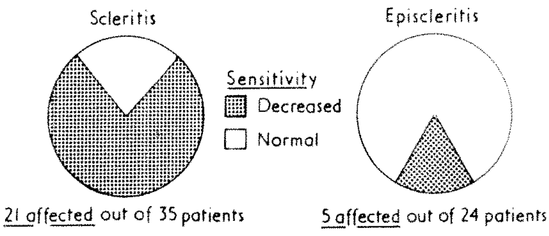

Fig. 4 *Number of patients with decreased corneal sensation in scleritis and episcleritis*

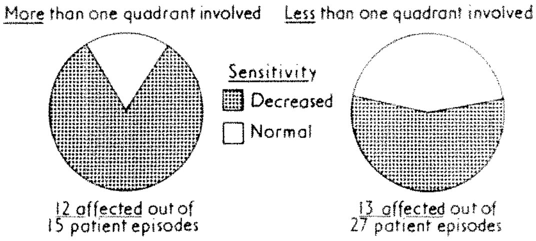

Fig. 5 *Effect of the number of quadrants involved by scleritis on reduction in corneal sensitivity*

In this aspect of the study patients with necrotising scleritis were omitted because profound loss of sensation in this condition occurs irrespective of the number of quadrants involved.

In all patients the corneal sensitivity returned to normal when the inflammation subsided except when a staphyloma resulted, and even then it did so if the staphyloma was small. Sclerosing keratitis appeared to have no effect on sensitivity.

Discussion

It is perhaps not surprising that corneal sensitivity is not often affected in episcleritis (5 patients out of 24), since this condition is a superficial inflammation and not likely to affect nerves that are lying at a deeper level. It does seem odd, however, that sensitivity is not affected more often in scleritis (21 patients out of 35). The explanation may lie in the anatomical arrangement of the corneal nerve supply.

Accounts of this vary in detail but the consensus is that it is derived from the long ciliary nerves (2 in number) and the short ciliary nerves (10 to 12 in number). All of them enter the eye by piercing the scleral coat posteriorly and passing forwards in the suprachoroidal space to the ciliary body to form the ciliary plexus in the ciliary muscle. Branches from this go to supply the ciliary muscle itself, the iris, the sclera, and the cornea. The corneal nerves divide and inosculate to form an annular plexus at the limbus. From the perilimbal plexus 60 to 80 nerves run towards the centre of the cornea, lying in its posterior third and dividing dichotomously as they go. A further network of nerves lies at the level

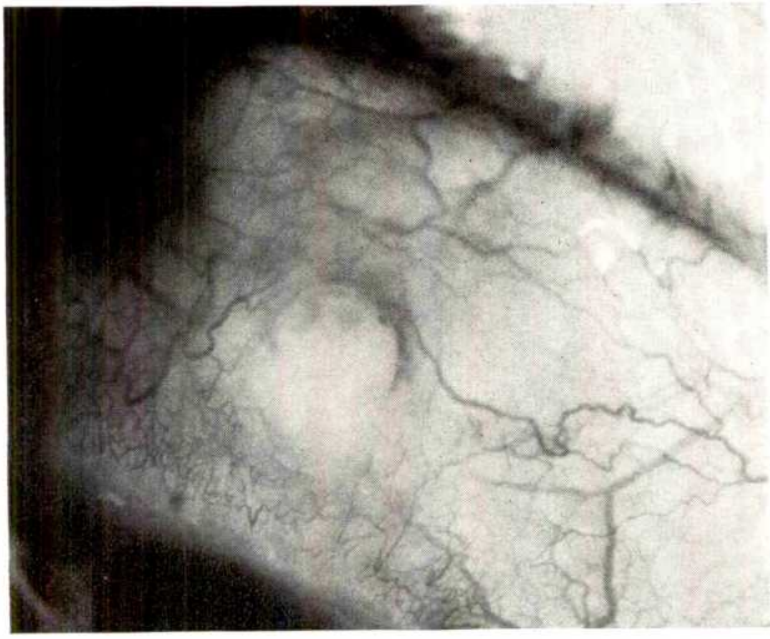

Fig. 7 *Case of acute necrotising scleritis*

of Bowman's membrane, which sends branches superficially between the epithelial cells (Thomas, 1955).

Any one corneal nerve supplies up to 25% of the corneal surface. From this description it follows that a lesion behind the perilimbal plexus would have to be extensive to have much effect on sensation if complete interruption of nerve conduction were to occur, and that even a lesion at the limbus or corneal periphery would need to be deep and extensive. It is known from experiments on rabbits (Zander and Weddell, 1951; Rexed and Rexed, 1951), in which different sizes of corneal incision were made, that sensation was lost only adjacent to the wound (Fig. 6). This would be explicable on the basis given above if the corneal nerve supply was similar in the rabbit.

If more than 1 quadrant of the sclera were to undergo inflammation the effect on corneal sensation would be more likely to occur, because adjacent nerves would be unable to compensate. This was found to be the case.

Necrotising scleritis is a rare and devastating form of scleritis which has important systemic associations, mainly acute connective tissue disease. In this study 5 cases of necrotising scleritis were examined, and in every one of them there was a profound loss of sensitivity in the corresponding area of the cornea irrespective of the number of quadrants involved. Fig. 7 shows a case of necrotising scleritis which went on to form an area of scleral necrosis that healed after high doses of systemic steroids, leaving an area of scleral ectasia (Fig. 8). Fig. 9 shows the corresponding sensitivity chart during the acute phase. There is an overall decrease in sensitivity in this eye, most marked in the corresponding quadrant. After resolution of this lesion the sensitivity returned to normal.

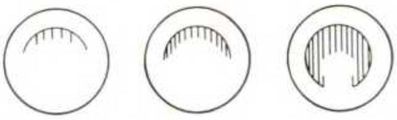

Fig. 6 *Loss of corneal sensation resulting from differing sizes of corneal wound*

Necrotising scleritis consists of a granuloma, the centre of which is necrotic, surrounded by an area of oedema and cellular infiltration. Nerves passing through the centre of the affected area would also become necrotic and would not recover. Nerves passing through sclera adjacent to the granuloma would suffer compression and temporary loss of function but would recover when the inflammatory process resolved with treatment. Permanent loss of sensation would result if the area of necrosis was large enough to make adjacent nerves unable to compensate.

The testing of corneal sensitivity in cases of episcleritis and scleritis is a worthwhile investigation. Significant decrease in corneal sensitivity indicates that the inflammatory process is more likely to be a

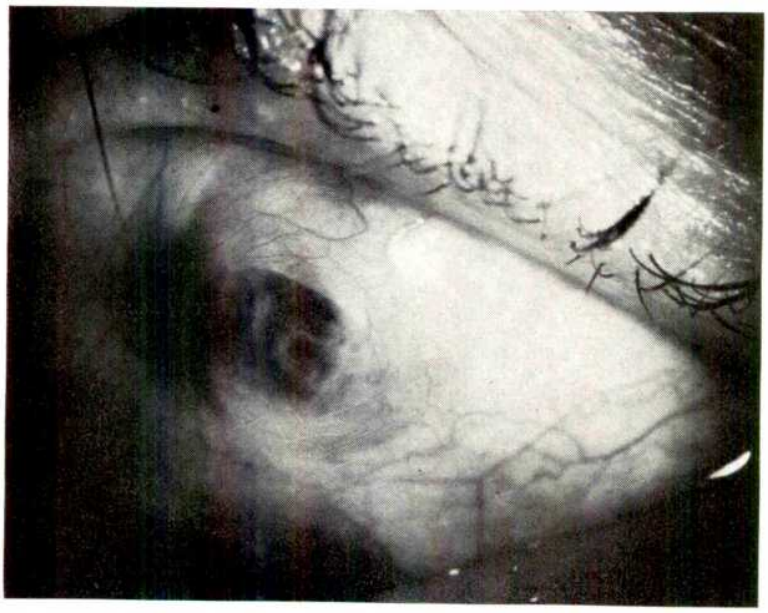

Fig. 8 *The same case after treatment in an inactive phase but showing scleral ectasia*

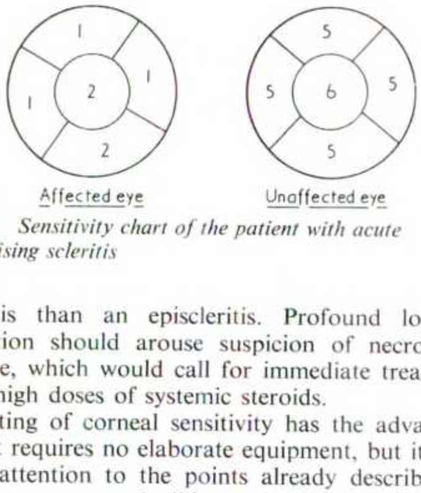

Fig. 9 *Sensitivity chart of the patient with acute necrotising scleritis*

scleritis than an episcleritis. Profound loss of sensation should arouse suspicion of necrotising disease, which would call for immediate treatment with high doses of systemic steroids.

Testing of corneal sensitivity has the advantage that it requires no elaborate equipment, but it does need attention to the points already described in order to get reproducible results. It is advisable to repeat the test at regular intervals to check the validity of the initial findings and as a monitor of the success or otherwise of treatment. Eyes in which the scleritis is resolving show a return to normal corneal sensitivity. This was so even in the presence of so-called scleral thinning. This latter state is usually one of increased scleral transparency (Rooney *et al.*, 1974), in which there is an altered arrangement of the scleral fibres. The only cases showing altered sensation in the quiescent state were those displaying large ectatic areas. These cases were often preceded by a necrotising scleritis, which had presumably damaged corresponding nerves beyond regeneration, and the intraocular pressure was often raised, which itself is known to decrease corneal sensation (Boberg-Ans, 1955).

I thank those surgeons who referred patients to the Scleritis Clinic, Mr P. G. Watson for suggestions with the study, and Miss D. Adamson for help with the typescript.

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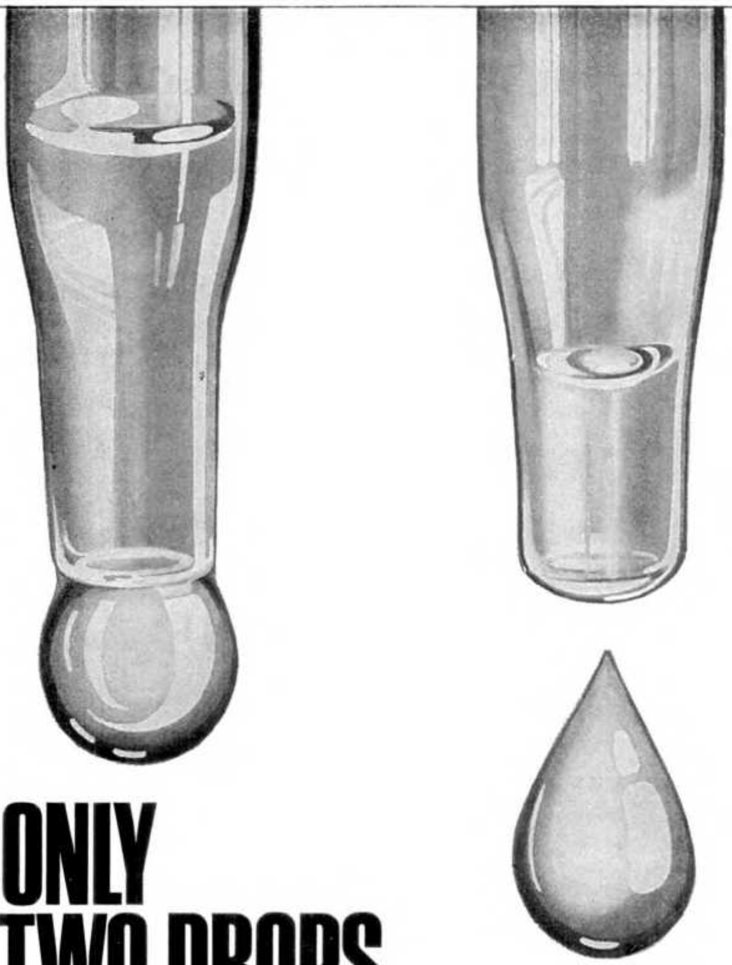

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The problem of uveitis in Bendel State of Nigeria: experience in Benin City

J. O. AYANRU
From the University of Benin Teaching Hospital, Nigeria

SUMMARY A review of 1987 patients with uveitis seen over an 11-year period in Bendel State of Nigeria has been undertaken; 56% of cases had a posterior/mid-peripheral uveitis, 15·1% a panuveitis, 21·5% an anterior uveitis. Acute anterior uveitis with classical symptoms was rarely seen. Its comparative rarity is presumably due to the absence of HL-A27 in Africans and altered immunological states from malaria and parasitic infections.

Identified aetiological factors in anterior uveitis were leprosy (1 patient), tuberculosis (1 patient), herpes zoster (16 patients), and onchocerciasis (3 patients). The great majority of cases of posterior uveitis were of presumed toxoplasmic origin. Further studies are needed to demonstrate its mode of transmission in a population in which toxoplasmosis is endemic. Forest onchocerciasis is not a major cause of uveitis in southern Nigeria in the same way as savanna onchocerciasis is in northern Nigeria. Syphilis seems to play no part in the causation of uveitis in southern Nigeria. Better diagnostic facilities are required to determine the role of sarcoidosis and other possible causative factors. Uveitis is a major cause of blindness in Nigeria.

Uveitis is a major cause of blindness in Nigeria (Olurin, 1973; Ayanru, 1974). It occurs mainly as a posterior uveitis or a panuveitis, anterior uveitis being relatively rare. This account reviews 1987 patients with uveitis seen over a period of 11 years, 1965–76, at the eye clinic of the Specialist Hospital, Benin City, Bendel State of Nigeria.

Materials and methods

The eye clinic of the Specialist Hospital, Benin City, was the only eye unit serving a population of 2¼ million people of the Bendel State of Nigeria during the period 1965-73. For varying periods it had one and sometimes two ophthalmologists only. In 1973 another eye clinic, at the University of Benin Teaching Hospital, was started. The Specialist Hospital eye clinic nevertheless remained the first port of call for patients with eye disease. Patients were also seen from neighbouring States of Nigeria, accounting for 1·5% of the 33 634 new ophthalmic patients who attended the clinic during the period under review. 1987 patients presented with uveitis (5·87% of total). Those who had endophthalmitis and traumatic uveitis have been excluded. Among the patients seen were soldiers with ocular injuries during the Nigerian civil war, when Benin City was a major base for the treatment of wounded soldiers.

Clinical examination was by ophthalmoscopy and biomicroscopy with a Haag Streit slit lamp before and after dilatation of the pupil with mydriatics.

All patients with uveitis had visual acuity tests, blood tests including a full blood count, erythrocyte sedimentation rate, Kahn or Wasserman test for syphilis, and a skin-snip examination for onchocerciasis. Over 65% of patients had a chest *x*-ray examination. Radiological investigations of sacroiliac joints, teeth, and sinuses were carried out in cases of anterior uveitis on 385 patients only. A Heaf test or Mantoux was done in cases presenting with a 'granulomatous uveitis'. The particular test done depended on which of the antigens was available at any one time. The Kveim, histoplasmin, toxoplasmin antigens and the Sabin-Feldman methylene blue dye test and uveal antigen are not available locally, nor are they readily available commercially elsewhere.

The mainstay of treatment was steroids—topical, systemic, or depot—and atropine. This regimen was combined with pyrimethamine in suspected cases of toxoplasmosis or diethylcarbamazine in proved cases of onchocerciasis. Occasionally the latter drug was used as a therapeutic test in cases in which skin snips were negative for onchocerciasis.

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Results

The most prominent symptoms were visual blurring in 1846 patients (92·9%), redness in 150 (7·5%), light intolerance in 79 (4·0%). 1256 patients (63·2%) on first reporting had a visual acuity of 6/60 Snellen or less, suggesting delay in reporting or inflammation at the posterior pole in and around the macula or considerable vitreous haze. In other cases it was a burnt out lesion at the macula with amblyopia and squint or secondary cataract and other complications that brought the patient to hospital.

In acute cases, in spite of evidence of intense anterior segment activity—keratitic precipitates flare—pain, ache, and photophobia were often not very prominent symptoms.

The average duration of symptoms before reporting was 1 to 2 weeks in cases of acute anterior uveitis. In posterior uveitis the interval varied with the literacy of the patients. Literate patients reported within 2 weeks. Other groups or those living some distance away from the clinic reported on the average at 3 months or when vision was completely lost.

The sites of the inflammation are as shown in Table 1. It must be admitted that in a large proportion of cases it was impossible to determine the site of the inflammation at the first visit on account of severe vitreous haze. Such cases were subsequently classified when inflammation had subsided. Cases of iridocyclitis following trauma were excluded in the group of anterior uveitis.

The male:female sex ratio was 2:1. There is, however, a high preponderance of males over females in all non-gynaecological clinics. No particular socioeconomic group was prone to developing uveitis. The peak age was 19 to 29 years (Fig. 1). One patient had a recurrence during pregnancy, while 2 had a first attack during pregnancy.

In spite of treatment 334 patients were blind (visual acuity of counting figures at 1 m and less) in one eye from a chronic posterior uveitis, 69 from a chronic anterior uveitis. Fifty patients and 4 patients were blind in both eyes from chronic posterior and chronic anterior uveitis, respectively.

Table 1 *Sites of inflammation*

No. of patients	*Site of lesion*	*% of total*
812	Posterior choroidoretinal lesion	40·9
300	Mid-peripheral	15·1
300	Panuveitis	15·1
429	Anterior uveitis	21·6
146	Unstated	7·3
1987		100·0%

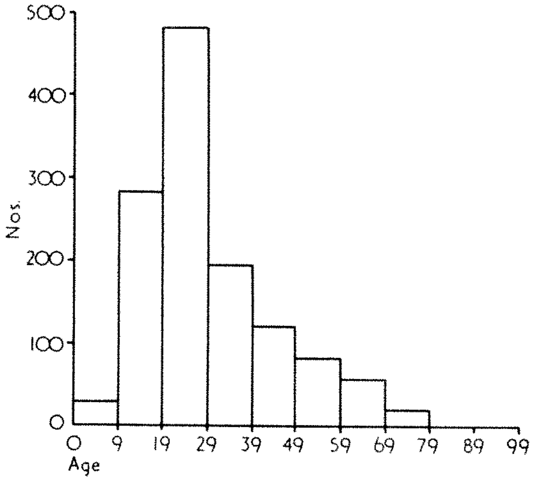

Fig. 1 *Distribution of uveitis cases by age*

There were no cases with positive serology for syphilis, nor was there radiological evidence of pulmonary tuberculosis in any of the patients. No cases of sarcoidosis were diagnosed. Positive skin snips for onchocerciasis (*Onchocerca volvulus*) were obtained in 6 patients, although in only 3 was ocular involvement diagnosed.

Discussion

The incidence of uveitis in the population studied is 5·87%. Uveitis causes the attendance of 8% of all new attendances at the University College Hospital, Ibadan (Olurin, 1973), the higher percentage in Ibadan probably reflecting the greater selectivity in a teaching hospital.

Uveitis is a major cause of blindness in one or both eyes in Nigeria (Olurin, 1973; Ayanru, 1974). The great majority of cases are of the posterior type (71·1%), acute anterior uveitis being relatively uncommon. In this series it accounted for 21·5% of cases.

The commonest and often the only presenting symptom is visual blurring. Pain, redness, watering, and photophobia are comparatively rare even in the presence of intense anterior chamber activity. The notable exception is traumatic uveitis, in which these symptoms may predominate. It is therefore not surprising that it is the literate patients—students, civil servants, literate housewives—that usually report early.

The investigation and hence the diagnosis of uveitis poses specific problems in this environment. Diagnostic facilities are limited and the specific antigens are not available. In view of the comparative rarity of acute anterior uveitis and the virtual absence of ankylosing spondylitis, *x*-rays of the sacroiliac joints are now seldom undertaken (Schlaegel, 1969). The Heaf or Mantoux tests, chest *x*-rays, skin snips for onchocerciasis, blood examination for eosinophilia, erythrocyte sedimentation rate, and serological tests for syphilis have been routine. The presence of ova of *Ascaris lumbricoides* or *Ankylostoma duodenale* in the stools of a patient with uveitis does not mean they cause the disease in this largely farming community with poor sanitation. Reliance has therefore been placed on the clinical picture (Woods, 1961), with emphasis on the location of the lesions (Perkins, 1961; Hogan *et al.*, 1959; Spalter and Len, 1966), and a therapeutic trial.

Thus it is not surprising that the cause of the disease often defies elucidation, although ecological and racial factors and knowledge of the pattern of diseases have greatly influenced diagnosis and hence possible treatment. But difficulty in detecting the cause of uveitis is not peculiar to this environment (Duke-Elder and Perkins, 1966; Schlaegel, 1969; Aronson *et al.*, 1968; Perkins, 1968; Saari *et al.*, 1975).

Toxoplasmosis is probably the single greatest factor in the causation of uveitis in the forest areas of Nigeria, in which Bendel State is situated. The fact that the clinical picture is one of a posterior uveitis, often recurrent, and near the macula, disc, or mid-peripheral in about 70% of cases (Ayanru, 1974), is highly suggestive. Chesterton and Perkins (1967) found a high percentage of presumed ocular toxoplasmosis in West African immigrants in London and a positive dye test in 89% of West African patients even without uveitis. The lesions were more frequently anterior to the equator than those seen in the indigenous population. Serological studies in the Delta area of Nigeria (Ludlam, 1965) and at Ibadan (Olurin *et al.*, 1972) confirm the endemicity of toxoplasmosis in Nigeria. The highest incidence in this series was in the second and third decades of life, 'which coincides with the period of greatest T cell activity as the body suddenly becomes aware of and mounts up a severe reaction against a previously tolerated antigen' (Desmonts and Couvreur, 1974). The patients who had a presumed toxoplasmic chorioretinitis in pregnancy may well have developed the lesions as a result of altered immunological competence, since most ocular toxoplasmosis is congenital (Perkins, 1973), and the infection may have lain dormant until pregnancy. None of the babies born to all three mothers had clinical evidence of disease. Depressed cellular immunity in pregnancy has been attributed to a serum factor (St. Hill *et al.*, 1973). Recurrences of ocular toxoplasmosis are more frequent during pregnancy.

Onchocercal uveitis—an iridocyclitis and peripheral chorioretinitis—and the degenerative posterior lesions of onchocerciasis seen in the savanna areas endemic for onchocerciasis (Hissette, 1932; Bryant, 1935; Ridley, 1945; Budden, 1955; Rodger, 1960; Neumann and Gunders, 1973; Bird *et al.*, 1976) have not been seen in this State, which lies in the rain forest area of Nigeria. Distinct epidemiological differences exist between forest and savanna onchocerciasis (Budden, 1963). In only 3 patients has onchocercal kerato-uveitis been proved here.

Syphilitic uveitis is not uncommon in northern Nigeria (Rodger, 1960). Syphilis is, however, rare in southern Nigeria, where yaws was endemic and shows cross-immunity against syphilis. None of the patients in this series showed serological evidence of syphilis.

Although only one patient with lepromatous leprosy and anterior uveitis was seen, examination of 179 patients at the Ossiomo Leper Settlement in the State showed that, of the 25 patients whose blindness was attributable to leprosy, 9 (36%) had iridocylitis. Eight of the 9 patients suffered from lepromatous leprosy and the ninth borderline lepromatous leprosy (Ayanru, 1975).

One patient with a granulomatous uveitis which failed to respond to steroid therapy was ultimately controlled with antituberculous drugs on the basis of a grade III positive Heaf test and the presence of mutton-fat keratitic precipitates. No primary focus was detected. Tuberculous uveitis is known to occur more in people with old or burnt-out tuberculosis than in those with active disease (Duke-Elder and Perkins, 1966).

Ogunlesi and Rankin (1961) and Femi-Pearce and Odunjo (1973) described cases of sarcoidosis in Nigerians in which uveitis was a feature. Although various aspects of African histoplasmosis have been documented (Clarke *et al.*, 1953; Duncan, 1958; Lucas, 1970) and reports of human brucellosis in southern Nigeria have appeared (Alausa and Awoseyi, 1976), there are no reports of ocular involvement. Sixteen cases of uveitis associated with herpes zoster ophthalmicus have been recorded. There is a relative infrequency of herpes zoster ophthalmicus affections.

Anterior uveitis, particularly acute, is commoner in Caucasian patients in London (Perkins, 1961, 1968), anterior uveitis accounting for 12 cases out of a population of 100 000 per year as compared to only 3 cases of posterior uveitis in the United States (Darrel *et al.*, 1962). The comparative rarity among Nigerian patients of acute non-granulomatous uveitis typically associated with various rheumatic diseases, classical ankylosing spondilitis, Reiter's disease, and Yersinia arthritis shown to be associated with an increased incidence of the histocompatibility antigen HLA-27 in Caucasian patients (Brewerton *et al.*, 1973; Ehlers *et al.*, 1974; Mapstone and Woodrow, 1975; Caffrey and James, 1973; Schlostein *et al.*, 1973; Aho *et al.*, 1973) can now be partly explained by the characteristic absence of the genetic marker HLA-27 among Africans and its presence among only 4% of Black Americans (O'Connor, 1974). These various conditions associated with acute anterior non-granulomatous uveitis are very rare in Nigeria and many parts of tropical Africa (Payet *et al.*, 1966; Greenwood, 1968). Greenwood (1968) has suggested that in Nigeria and other African countries the relative rarity of connective tissue and autoimmune diseases may be partly explained by the altered immunological state of Africans through malaria and various parasitic infections in the region. Huldt *et al* (1973) and Strickland *et al* (1973) have reported immunosuppression in mice infected with toxoplasma organisms, and there are indications that toxoplasmosis, like viral hepatitis, can cause immunosuppression (O'Connor, 1974). Both toxoplasmosis and viral hepatitis are endemic in Nigeria (Ludlam, 1965; Edington and Gilles, 1969; Olurin *et al.*, 1972).

Iridocyclitis due to cerebrospinal meningitis (Budden, 1952), which latter disease often rages in epidemic form in northern Nigeria, is rarely seen in southern Nigeria. No cases were recorded here. Gonorrhoea is common and on the increase. Its role in the causation of uveitis in Nigeria is undetermined.

Unlike the experience of Freedman (1973) among South African Bantu children no case of sympathetic ophthalmitis was recorded in this series in spite of the high incidence of perforating ocular injuries and the usual habit of reporting late in hospital. Several factors other than racial have a part to play in the genesis of this condition (Mann, 1961). No patients with heterochromic cyclitis or the Vogt-Koyanagi-Harada syndrome have been seen, nor have cases of uveitis induced by dexamethasone sodium sulphate been encountered (Martins *et al.*, 1974).

In the absence of a precise ascertainment of the cause in most of these cases the mainstay of treatment has been steroids—depot, topical, or systemic—with mydriatics. Diethylcarbamazine tablets and topical hetrazan have been used in the isolated cases of onchocerciasis as topical hetrazan is of proved value (Ben-Sira *et al.*, 1970).

Pyrimethamine and/or sulphadiazine were not given in addition as a routine in suspected cases of toxoplasmosis because no difference has so far been found here in the recurrence rate or healing of lesions in patients so treated. The dangers of giving steroids without antimicrobial therapy have been highlighted (Editorial, 1976), but the persistent leucopenia seen in the few patients so treated, particularly in an environment where patients cannot be relied upon to return for a check-up once their ocular disability seems less, has influenced this mode of treatment. Perhaps this regimen can also be justified on the basis of O'Connor's report (1974) that both pyrimethamine and sulphonamide produced disappointing or unreliable results in human ocular toxoplasmosis, especially when the lesions were large or of long duration. They were useful in cases of acute small lesions. Most of these patients reported late in hospital. Neither clindamycin nor BCG have been used in the treatment of our cases of presumed ocular toxoplasmosis (Cahill, 1974). No cases of uveitis have been sufficiently intractable to warrant the use of immunosuppressive agents (Martenet, 1972) or cryotherapy (Aaberg *et al.*, 1973).

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An introductory report on the use of Bioplast in ophthalmic surgery

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SUMMARY Bioplast is an excellent material for implants. It lends itself readily to cutting and suturing and is easily applied. It is highly suited to ophthalmic surgery. It has the great advantage of having no antigenic properties and is quickly absorbed. Our cases recovered without complications, and the results were satisfactory both functionally and cosmetically. For these reasons we recommend Bioplast in ophthalmology.

Conjunctiva may be replaced by many other tissues, as reviewed by Collin (1975). In 1955 Gerendás prepared a plastic-like film, Bioplast, from human or animal fibrin by compression moulding of fibrin and glycerol. It is currently marketed by Ethicon Ltd, Edinburgh, under the registered name Biethium. It is a translucent, yellowish-brown, flexible preparation lending itself readily to implantation (Gerendás, 1959). Horvath *et al.* (1969) stated that by prior heat-treatment Bioplast loses its antigenic properties, and it causes neither fever nor an immune response. It readily covers the tissues and allows natural or spontaneous healing to occur unobstructed. Bioplast is not incorporated into the repair. By its use regenerative processes in the surrounding tissues are stimulated. Having fulfilled its task, Bioplast is absorbed by enzymatic cellular digestion (Bagdy *et al.*, 1963; Capperauld *et al.*, 1977).

Successful Bioplast implantations have been carried out in various fields of surgery and for a variety of conditions: in neurosurgery (Afra (1960) used Bioplast as a dural substitute); coxitis tuberculosa (Kovács and Gerendás (1961) as a cup prosthesis over the hip joint); liver buffers (Drobni and Dóczy, 1962; Drobni, 1965 and 1969; Wood *et al.*, 1976); osteomyelitis (Winter and Papp, 1964); surgery of the nasal septum (Gyeney, 1973) and the maxilla (Kovács and Kerényi, 1976); and in the management of stress incontinence of urine in women (Horn *et al.*, 1975).

In ophthalmic surgery Grósz *et al.* (1967, 1968, 1976) were the first to use Bioplast for indenting the sclera in retinal detachment operations. Later Tapasztó (1973, 1975) reported the successful application of Bioplast to caustic lesions of the conjunctiva and in the surgical treatment of pseudopterygium.

Materials and methods

Since July 1975, 21 operations have been performed using Bioplast. In 7 cases it acted as a substitute for conjunctiva, and in 14 it was implanted into the edge of the lid.

In 5 cases Bioplast was used for the surgical treatment of recurring pterygium. From a gamma-irradiated, double over-wrapped piece of Bioplast measuring 10×10×0·2 mm a small portion is cut to cover the bare area of sclera after removal of a pterygium and secured with 6/0 catgut or 20/22 silk sutures. Bioplast has also been used in total-surface symblepharon caused by silver nitrate and following extirpation of a conjunctival papilloma.

Intermarginal plastic surgery using Bioplast was carried out in 14 cases, among which 13 were van Milligan operations for entropion. Bioplast was used here instead of the conventional oral mucous membrane.

Results and discussion

Our experience indicates that Bioplast is easy to handle, as it lends itself readily to cutting and suturing. On the 2nd to 4th day after implantation in the conjunctiva it becomes veined and finely granulated, accompanied by the discharge of a small amount of greenish-yellow secretion. From the 5th to 6th day it becomes increasingly difficult to distinguish the implant from its environment, and its borders with healthy conjunctiva are indicated

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only by the sutures. After 30 days the implant cannot be recognised even with a slit lamp.

In no case did we observe infection, rejection, or an allergic reaction. Recovery was perfect both functionally and cosmetically. No recurrence occurred during the 4 to 12 months of observation.

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Bee and wasp stings of the eye. Retained intralenticular wasp sting: a case report

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SUMMARY Two different stages should be considered in the management of bee and wasp stings to the eye. The first is the acute stage of activity of the specific insect venom on the structures of the eye. The reaction of the eye to the particular insult is considered here in regard to the anterior and posterior segments of the eye. The second stage is that of the retained intraocular foreign body, the inert sting. Little is known about the reaction of the eye to the presence of the chitinous sting and its effect on the structures of the eye. We report a follow-up study of a sting retained for 28 years, and emphasise the benign and quiescent course of the case. Guidelines for treatment and management in such cases are described.

'Damage to the eye caused by insects is frequent. Their sting may cause considerable reactions and leucomata of the eye' (Van Horn, 1948). The list of foreign bodies which may enter the eye is endless. Some of these are typical and common to agricultural surroundings. Insects—their wings, legs, spines, or stings—are common intraocular foreign bodies in these surroundings as well as in some tropical regions. Occasionally stinging insects introduce into the eye part or parts of their bodies, as do wasps and bees (Duke-Elder, 1940).

We discuss here the management and treatment of such foreign bodies and report on a long-term follow-up study of retained intraocular wasp sting.

Case history

A 48-year-old man was examined routinely in our department for the purpose of changing his glasses. On examination his visual acuity was found to be: right eye 6/9, with correction −0·5 sph., −0·5 cyl. 140°; left eye 6/6, with correction −1·5 sph., −0·5 cyl. 90°. Intraocular tension was 14·5 mmHg in both eyes. His left eye was quiet, refracting surfaces were clear, and there were perfect fundi. In the centre of the cornea of his right eye a fine scar was found, and in the centre of the lens in front of it an insect sting was seen protruding into the anterior chamber. The foreign body appeared to resemble a needle, and the area of penetration was a circular opacity, confined to the anterior lens capsule (Fig. 1). No signs of iritis were found. The pupil was round and responsive to light. The lens was clear in all its other parts, the fundus was normal, and no other signs of disease were seen.

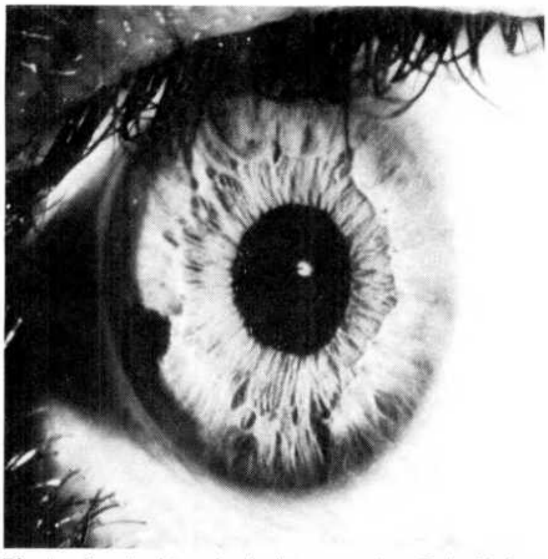

Fig. 1 *Retained intralenticular wasp sting. Embedded sting in the centre of the lens protruding into the anterior chamber*

The patient said he remembered having been hit and stung by a wasp on his upper right eyelid 28 years previously. This resulted in so severe a reaction that the patient was in hospital for several days

From records made at the time which we received from the hospital we obtained the following additional information. The patient was in hospital from 31 July to 8 August 1948 suffering from oedema of

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the conjunctiva as a result of a wasp sting in the right eye. Round the sting was a white corneal infiltration and a lack of epithelial covering.

After several days in hospital a marked improvement was noted, with regression of the oedema and recovery of the epithelium. On discharge from hospital some ciliary injection and a slight infiltration of the right cornea remained. In this condition the patient was referred to the outpatient treatment.

No mention was made in the records of the sting having remained embedded in the lens. In subsequent years the sting did not cause any inflammation or subjective complaints by the patient except for a slight lessening of visual acuity in the affected eye.

Discussion

The frequency of wasp and bee stings and the species of wasp or bee involved depend on the geographical location and the season of the year. In the act of stinging, these insects introduce two bodily components into the eye: the chitinose sting and the specific venom which the sting contains. The venom acts as a toxic agent, and the sting itself has a mechanically damaging effect on the structures of the eye (Grant, 1962; Bucherl and Buckley, 1971).

Bee and wasp stings of the eye have been well discussed by Lewin and Guillery (1913), Young (1931), and Kranning (1955). The sting, a modified ovipositor in the female, usually lies in the abdomen and is typically provided with toothed lancets and poison glands containing venom. Its toxic action is presumed to be due to several biological amines (Welsh, 1964; Owen, 1971). This mixture of compounds acts as a potent protoplasmic poison, which produces a violently painful oedematous reaction, local as well as general. Several active components in this mixture have been found, and the specific composition of the venom is known to differ in the bee and the wasp. Some biologically active components which have been isolated in bee venom are neurotoxin, haemolitin, mellitin, hyaluronidase, phospholipase A, and histamine. Wasp venom contains acetylcholine in addition. Wasp stings appear to be more painful and more serious in nature than bee stings. From the practical and clinical points of view, however, bee and wasp stings may be considered together.

Reaction of the eye

ANTERIOR SEGMENT

The cornea. The most serious reaction of the anterior segment has been encountered in cases in which the sting entered the cornea. The victim suffers much pain and photophobia associated with clouding and swelling of the cornea itself. Iritis, hypopyon, and mixed conjunctival and ciliary injection develop. Typically, in wasp stings bullous keratitis has been known to persist for many months. Characteristically, a striate keratitis and pathognomonically, a fine network of ridges in the corneal epithelium appear surrounding the retained sting. During the height of the reaction the cornea may become heavily infiltrated at the site of the sting. Histologically, necrosis of cells and a large collection of leucocytes are to be found in the immediate neighbourhood of the sting or at the place of inoculation of the venom. Thereafter the inflammatory reaction gradually subsides. However, the area of the cornea surrounding the sting commonly remains permanently clouded and vascularised. Gradual complete clearing and recovery of normal vision are to be expected (Khachaturova, 1960) even though the sting remains in the cornea. Damage to the eye, specifically to the cornea, results in an irregularity of the corneal surface which may require an astigmatic correction to improve vision, as is seen in our case.

The iris. The iris shows great vasodilatation, with several haemorrhages and leucocytic infiltration, but no necrosis.

The lens. The lens has been known to develop small grey opacities on the anterior surface, even when not mechanically injured by the sting. Anterior polar cataract may appear. Some degeneration of the epithelium of the lens capsule has been reported, with accumulation of fluid between the capsule and the lens substance, followed by proliferation of the intact epithelium (Huwald, 1904).

POSTERIOR SEGMENT

There are some reports of possible neurotoxic effects on the retina and the optic nerve, though it is odd that posterior segment complications have usually not been associated with stings to the eye specifically but to the lids or elsewhere in the head. Optic atrophy and papillitis secondary to bee sting have been described (Walsh and Hoyt, 1969; Goldstein and Woltman, 1960). Papilloedema of 1 dioptre and much retinal venous engorgement with normal visual acuity have been observed 9 days after bee stings (Goldstein and Rucker, 1964). Retrobulbar neuritis has been described following wasp stings (Konstas and Nikolinakos, 1965). These severe reactions seem to be related to the venoms carried with the sting and not to the sting itself.

Clinical and experimental studies

From clinical observations and experiments on animals it is evident that we must consider two different effects on the eye: the reaction to the specific venom and the effect of the chitinous sting. From experimental studies on rabbits (Strobel, 1931) it has been concluded that, once the toxic material is inactivated from the bee or wasp sting, it becomes completely inert and can be retained in the cornea or anterior chamber without trouble. It has been shown that the venom is responsible for the severe inflammatory reactions, that the severity depends on the amount of venom, and that it is unimportant whether or not the sting itself remains embedded in the eye. As to the presence of the sting in the eye over a prolonged period, there are few relevant reports and almost no follow-up studies. But one case followed up for 21 years has been described (Strobel, 1950), in which a bee sting was retained within the cornea, protruding into the anterior chamber, with no signs of inflammation. In our case the follow-up was for more than 28 years without any signs of inflammatory activity.

Treatment

ACUTE STAGE

As soon as possible after the patient is stung therapeutic action must be taken against the activity of the venom. Some therapeutic suggestions have been made. Repeated paracentesis may be employed in cases in which the sting has entered the anterior chamber (Strobel, 1950). However, it seems that the correct use of modern anti-inflammatory medical treatment will control the inflammation and will prevent possible later complications. Use of antibiotics, antihistamines, and local and systemic corticosteroids is imperative according to the severity of the inflammation in each particular case.

RETAINED STING

The presence of the sting as a retained intraocular foreign body is a problem for the clinician. Injury as a result of injudicious and awkward attempts at its removal may cause permanent damage to vision and even occasionally lead to the loss of the eye. If the only sequela of being stung is retention of the inert sting, no surgical intervention is advisable.

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Book reviews

Current Concepts of the Vitreous, Including Vitrectomy. Edited by K. A. GITTER. 1976. Pp. 289, figs, tables, refs. Mosby, St. Louis (London, Henry Kimpton) (£20·50)

Vitrectomy via the pars plana is arguably the most exciting recent advance in ophthalmology, and these proceedings of a tutorial conference held in New Orleans in April 1975 serve to underline the established place of this new technique in our surgical armamentarium. Most of the best-known workers in the field of vitreous surgery contributed to its pages with the notable exception of Dr Robert Machemer, of Miami, whose inspiration and influence on the evolution of vitrectomy are nevertheless evident throughout.

The conference considered vitreous anatomy and pathology, preoperative clinical and ultrasonic evaluation of cases, the vitreous and cataract surgery, and techniques of open-sky and pars plana vitrectomy. The use of the Douvas Rotoextractor was described and illustrated in particular detail, and results from various centres are documented. Diabetic vitreous haemorrhage and ocular trauma were considered in depth, though few hard facts emerged as to how and when the lens should be removed in diabetic patients with vitreous haemorrhage, for example, or whether fibrous proliferation can be prevented by early vitrectomy following trauma.

The contributors emphasised that the vitrectomist must combine a facility in microsurgical technology with expertise in all aspects of retinal surgery. Certainly, the chapters and round-table discussions on operative and postoperative complications should be read by anyone contemplating performing the 'occasional' vitrectomy; they make suitably harrowing reading. D. MCLEOD

1st International Congress on Vision and Road Safety. 1976. Pp. 500, figs, tables, refs. Prevention Routière Internationale. Lines, Montlhery (No price)

This is the report of an international congress on vision and road safety which was held in France in 1976. The meeting considered all aspects of safety in relation to the driving of mechanically propelled vehicles. The standards for driving vary greatly in different countries, and there is no consensus of opinion on what is a suitable visual standard for driving.

The meeting discussed many different aspects of the visual standards required for safe driving, and it is to be hoped that these discussions among representatives of different countries will result in some standardisations of the visual acuity which should be required for driving motor vehicles in all parts of the world. S. J. H. MILLER

Intraocular Lenses. Transactions of the University of Illinois Symposium on Intraocular Lenses. By T. WILENSKY. 1976. Pp. 182, figs, bibliography. Appleton-Century Crofts, New York (Prentice/Hall International, Hemel Hempstead) (£13·20)

The book opens with a history of pseudophakia and a chapter follows on 'Indications for Intraocular Lens Implantation' by Norman Jaffe. There follows a chapter on Surgical Technique as applied to the various types of implant—the Choyce Mark VIII anterior chamber implant, the Worst Medallion lens, the Fyodorov lens, the Copeland iris plane lens, and the Binkhorst iris-clip lens. The selection of lenses is discussed and the question of intracapsular versus extracapsular cataract extraction is reviewed and also the matter of the implanting of lenses in children. There follows a valuable section on complications of intraocular lenses and their management. Surgical complications are discussed by Drews, glaucoma by Galin, cystoid macular oedema by Jaffe, and uveitis and corneal dystrophy by Choyce, and retinal detachments by Goldbaum. Medicolegal considerations in intraocular lens implantation are reviewed, and Sherwin Fox describes some experimental lens implantation carried out in animals. Finally, there is a round-table discussion by the panel, where many points in technique are freely discussed. S. J. H. MILLER

Documenta Ophthalmologica Proceedings. Vol 12. Symposium on Medical Therapy in Glaucoma. Edited by E. L. GREVE. 1976. Pp. 137, figs, refs. Junk, The Hague (Dtch glds 40)

This symposium was organised to provide the general opthalmologist with recent knowledge about medical therapy in glaucoma. The treatment of glaucoma simplex is still limited to the lowering of intraocular pressure by increasing the outflow or diminishing the secretion or both.

The opening chapter is on factors influencing the concentrations of a drug and its site of action in the eye, and this leads to a discussion on membrane technology as applied to the therapeutic possibilities of controlled delivery of drugs. The actions and uses of parasympathomimetic drugs in glaucoma are discussed at some length, and this account is followed by a chapter on cholinergic drugs. There is an interesting contribution on experiences with Ocuserts and further sections on the adrenergic preparations and their possible use in the treatment of glaucoma. Finally there are chapters on the ocular hypotensive effect of atenolol and oxprenolol, on the criteria for the initiation of treatment in patients with suspected glaucoma, and the general management of glaucoma patients both medical and surgical.

The areas where advances have been made are the continuous zero-order release of drugs which avoid overdose-underdose, employ a lower quantity of the drug with a better control of night pressure, and the avoidance of the psychological effects of the use of eye drops 4 times a day. The other area which shows signs of advancement is the use of beta-blocking drugs, which may prove a valuable aid to non-miotic therapy if tachyphylaxis can be overcome. Each chapter has a useful bibliography. This slim, well-written volume will not overtax the busy practitioner. At the same time it will bring him up to date in the medical therapy of glaucoma, indicating where such therapy is likely to be modified as a result of investigations and research. S. J. H. MILLER

Cranial Computerized Tomography. Edited by W. Lanksch and E. Kazner. 1976. Pp. 478, figs, tables, refs. Springer Verlag, Berlin (DM78)

This book is a collection of papers read at the Third Internation Symposium on Computerised Tomography held in Munich in June 1976. Most of the contributors are from Germany and Switzerland, with a few invited guests from other continental European countries and the United States.

The first section, on physical principles, is clear, well illustrated, and forms an excellent introduction for clinicians wishing to familiarise themselves with basic aspects of the technique. There is also a good section on new technical developments. In the other eight sections most anatomical and pathological areas are covered. The standard of the individual papers is generally high, and the weaker articles probably reflect the relative inexperience of the authors. The sections on neuro-paediatrics, brain atrophy-epilepsy-demyelinating and degenerative diseases, and brain oedema make interesting and informative reading.

In general, the width of material covered makes it a useful guide for those clinicians wishing to either acquaint themselves with the technique or to have as a reference volume. D. TAYLOR

Fison's Retinal Detachment Surgery. By A. Lim Siew Ming. 1977. Pp. 88, figs. P.G. Medical Books, Singapore (No price)

This is a very good book because it has a clear purpose which it fulfils admirably. That purpose is to supply a practical guide to the management of retinal detachment. It is clearly written in a concise form with many short headings so that specific points can easily be discovered. Many excellent colour illustrations and relevant diagrams are so well integrated with the text that the information imparted is more practical than found in many longer books. The author speaks from wide personal experience; his style is therefore didactic rather than scholastic and personal rather than academic—an approach that is exactly correct for a handbook on retinal surgery.

The book is divided into ten chapters: Techniques of Examination and the Binocular Indirect Ophthalmoscope; Scientific Basis of Retinal Detachment Surgery; Cryotherapy, Diathermy and Photocoagulation; Local Plombage and Encircling Techniques; Drainage of Subretinal Fluid; Prophylaxis; Special Problems; Vitreous and Vitreous Surgery; Surgical Complications, Avoidance and Treatment, Recurrence of Detachment; and Postoperative Management and Follow-up.

Such a publication demands good team work, and the editor must be given due credit for the excellent layout of the book. It is a hallmark of the author's philosophy in running a specialist department that the chief should not attempt to maintain a monopoly but give his juniors their heads. This book is based on courses in retinal detachment surgery, originally delivered by his unit in London. It is typical of the author's generosity that in the preface he refers to his registrars who initiated and planned these courses. R. K. BLACH

Current Contents in Cataract Surgery. Selected Proceedings of the 4th Biennial Cataract Surgical Congress. 1977. Pp. 672, figs, tables, refs. Mosby, St. Louis (London, Kimpton) (£40·25)

In the past 6 years there have been radical changes in the management of cataract. New techniques, such as phacoemulsification, lens fragmentation and aspiration, anterior vitrectomy, and intraocular lenses, have greatly increased the range of cataract surgery. This book consists of selected papers and discussions of the Fourth Biennial Cataract Surgical Congress, and the views of the leading American surgeons on a wide range of these newer techniques and of the perennial problems associated with surgery of the lens are presented in a colloquial but very readable form. J. H. DOBREE

Obituary

E. K. R. Thomas, MB, ChB, FRCSEd, DOMS, 1899-1977

Kenneth Roy Thomas, who died on 6 July, was born at Llanybyther in 1899, and graduated in medicine at Edinburgh in 1921. In 1924 he was appointed ophthalmic surgeon to Swansea General and Eye Hospital, a post which he held until 1964. He was secretary of the Swansea Division of the BMA from 1929 to 1933 and chairman from 1938 to 1941. In 1962 he was made a Fellow of the BMA. He was a member of the Oxford Ophthalmological Congress and a past president of the Western Society and the Welsh Edinburgh Graduates Association. He was a past president of the Carmarthenshire Society and a member of the Swansea University College Council. He is survived by his wife, Gwyneth, and by his son.

Notes

11th Hellenic Congress of Ophthalmology

15–18 June 1978

The Congress will take place in Chalkidiki (Kassandra peninsula), Greece, on 15 to 18 June 1978. Its subject will be 'Ocular Tumours'. Simultaneous translation in Greek, English, French, and German. Further details from 11th Hellenic Congress of Ophthalmology, PO Box 497, Thessaloniki, Greece.

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Edited by R. N. Maini and E. J. Holborow

A supplement to the Annals of Rheumatic Diseases based on workshops to promote wider knowledge of laboratory methods available for measuring circulating immune complexes and anti-DNA antibodies has recently been published.

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Section B is divided into three parts. The first contains the details and evaluation of a joint experiment for the detection of anti-DNA antibodies conducted by 12 laboratories in Europe and USA on a panel of 8 sera. The following laboratories were represented: Aarden (Amsterdam), Barnett (Los Angeles), Federlin (W. Germany), Hughes (London), Johnson (Taplow), Lambert (Geneva), Maini (London), Schur (Boston), Steward (London), Stollar (Boston), Tan (La Jolla), Talal (San Francisco). In the second part the methods used by the participants are described. In the third, Dr Barnett, who has a long association with this field, presents a personal view on the present state and future developments in the clinical application of tests for anti-DNA antibodies.

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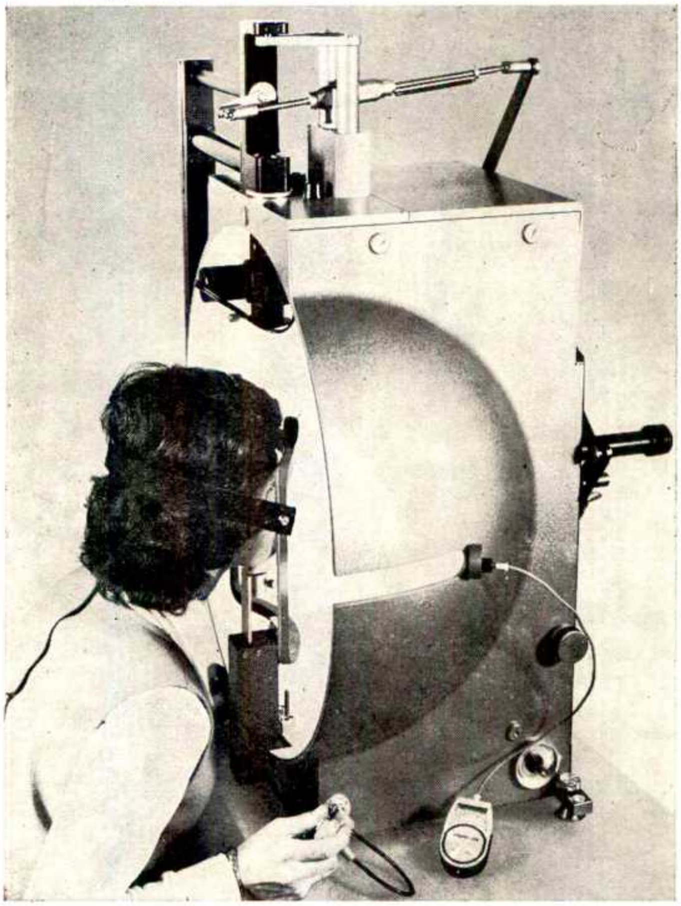

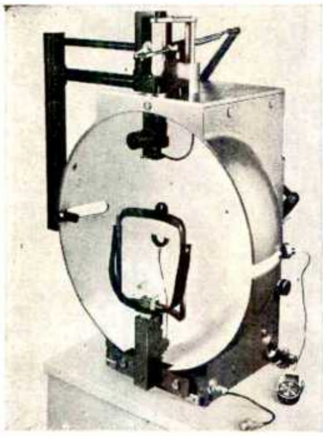

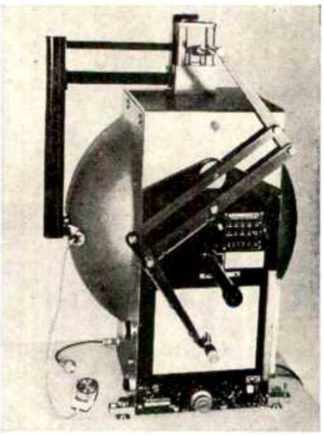

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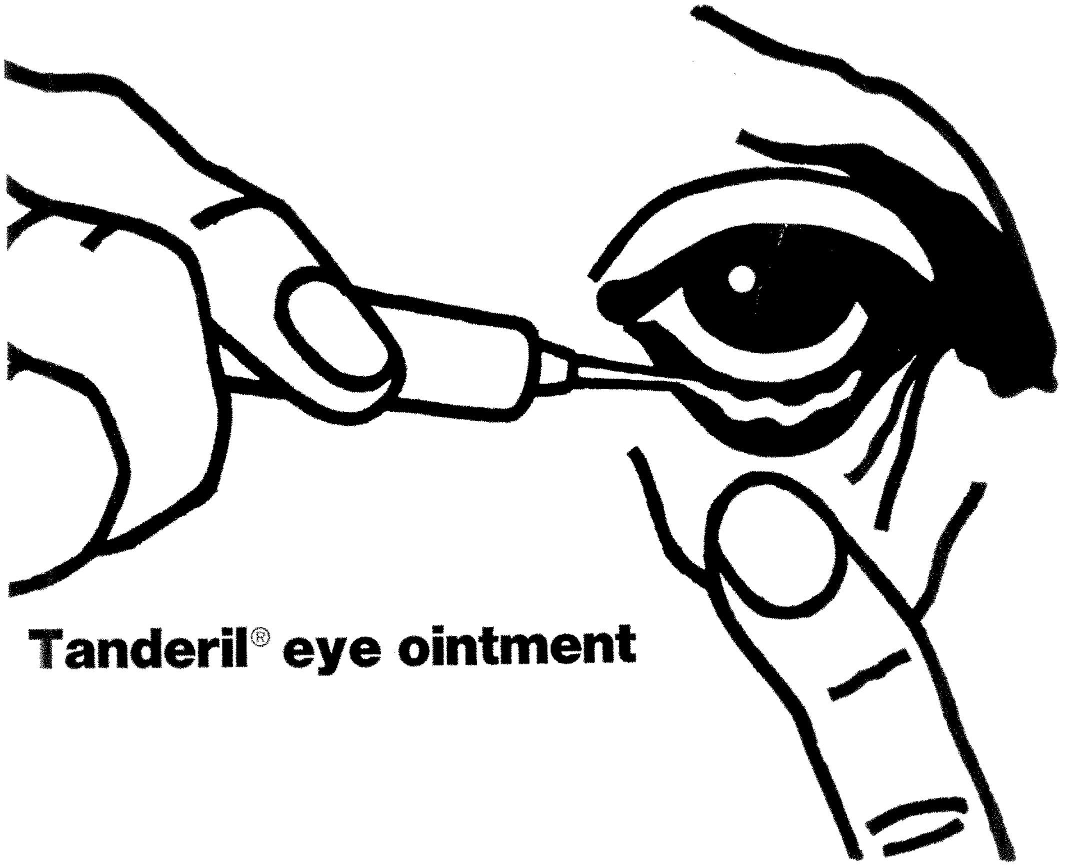

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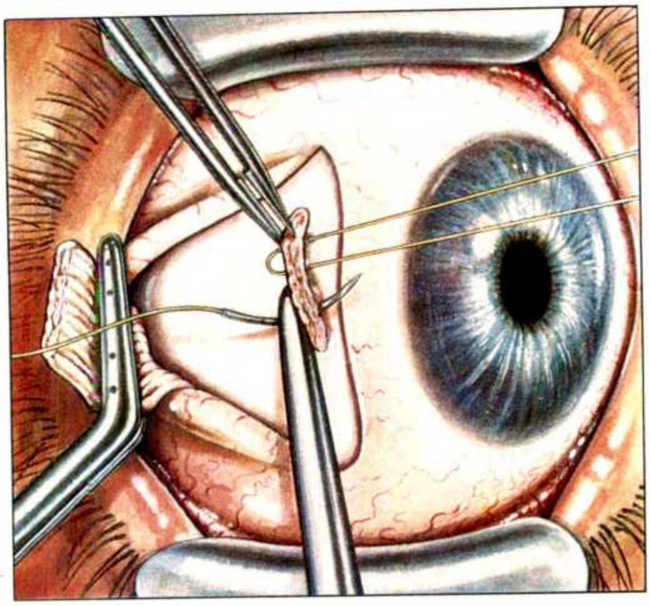

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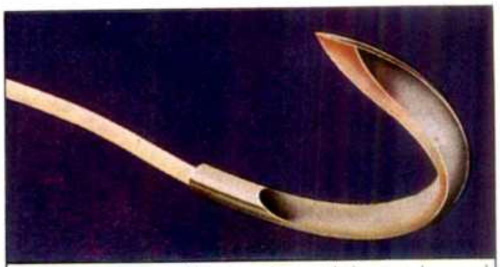

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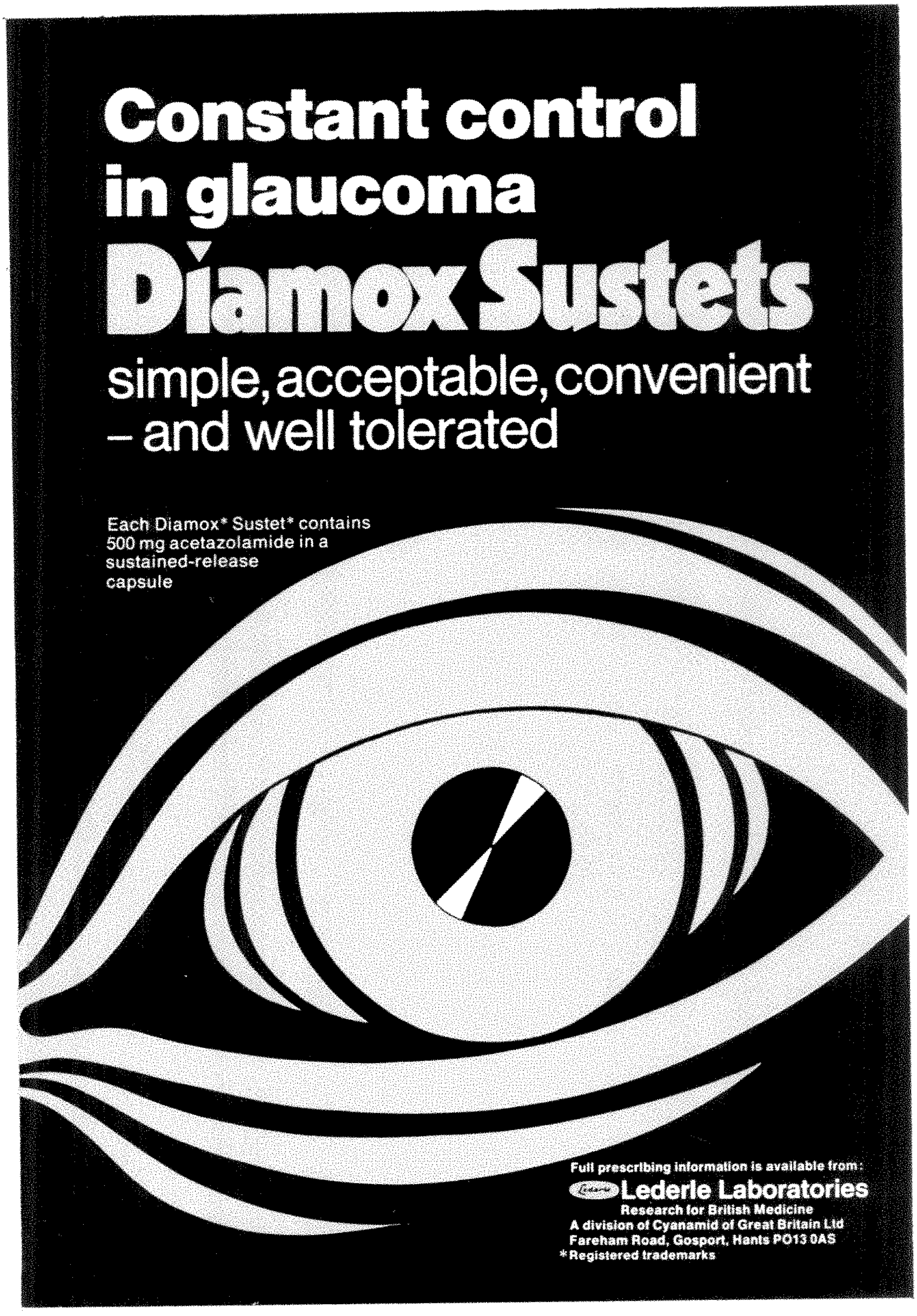

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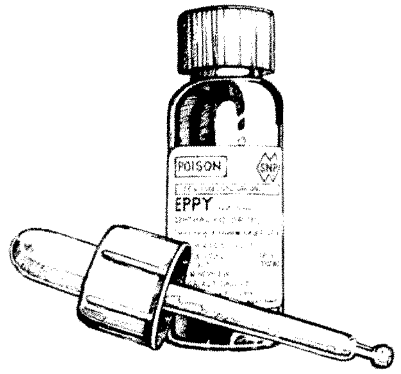

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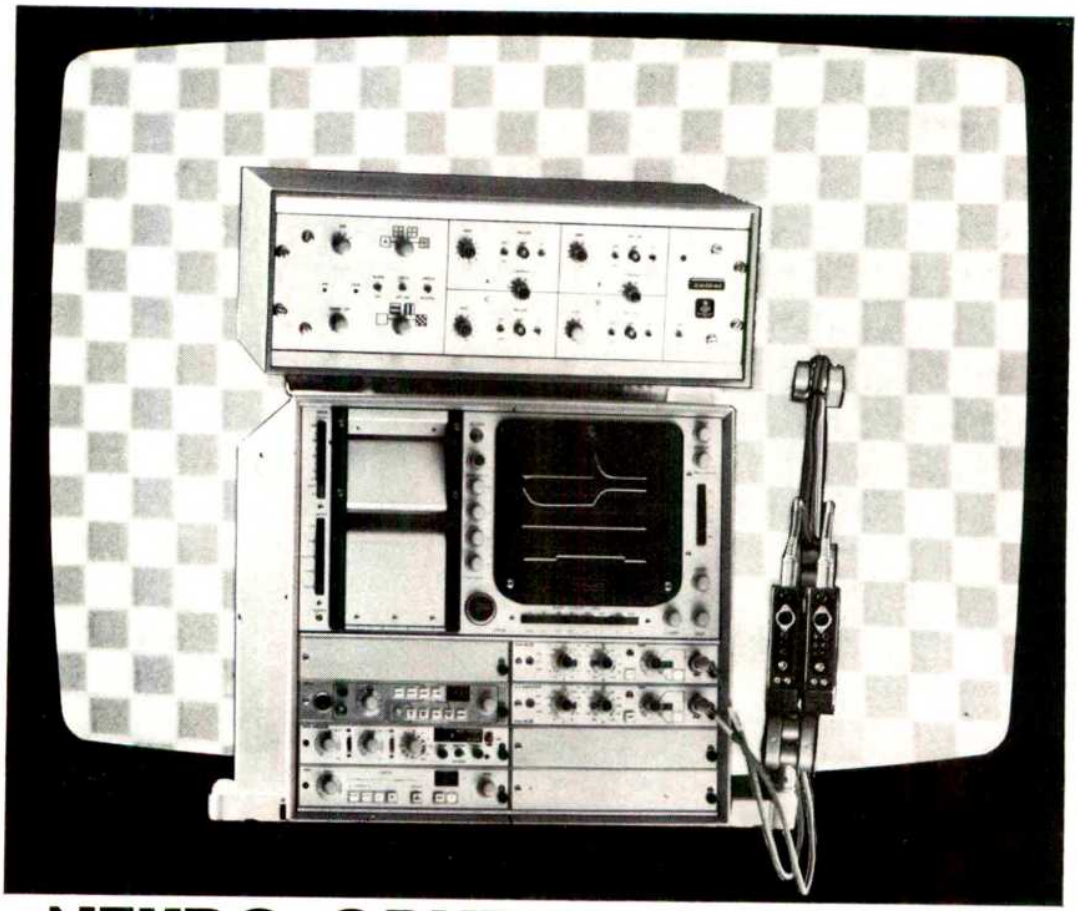

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(1) Linn M.L. and Jones L.T.
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British Journal of Ophthalmology, 1977, **61**, 667

Editorial: Ocular hypertension

Ocular hypertension exists in an eye where the intraocular pressure is above 21 mmHg but where there is no other detectable pathology. The incidence of ocular hypertension in the United Kingdom is approximately 10 times greater than that of open-angle glaucoma, and only a small proportion of these patients, between 5% and 8%, eventually develop glaucoma. The question then arises as to which patients with ocular hypertension should be treated and which should be kept under intermittent observation. In this respect it is not considered safe to leave any patient with a high pressure untreated unless adequate facilities for regular perimetry and observation of the optic discs are available. On the other hand no form of treatment is without side effects, and the risk and inconvenience of these to the patient must be weighed against the risk of damage to the optic nerve head.

Certain factors have now been identified to guide us in the management of these cases. The state of the optic disc is the single most important criterion, and if the disc gives rise to any suspicion it is safer to treat the patient. Warning signs include a large or enlarging cup disc ratio; a vertical oval cup; asymmetry between the two optic discs greater than 0·2, and a sector haemorrhage on the disc. Age is also important. Studies have shown that the chance of patients with ocular hypertension developing a field defect increases with age. Similarly patients with an intraocular pressure over 30 mmHg are at greater risk than those with pressures at lower levels. The presence of a family history of open-angle glaucoma also predisposes to the disease. So treatment should be started in any patients with discs that arouse suspicion, especially if the patients are in the older age groups or their intraocular pressure in the higher ranges.

Regular observation is safe for the younger patients with healthy optic nerve heads. It is the people in between who pose problems. In this field recent researches have been directed towards discovering prognostic indices which will help to differentiate, before damage occurs, those patients destined to develop glaucoma. Studies have established an association between diabetes mellitus and glaucoma and suggested possible antigenic links with the disease. One recent survey shows that patients with ocular hypertension who have either of the HLA antigens B12 or B7 are at greater risk of losing field. The results of the response to a single instillation of adrenaline may also prove important in prognosis. The long-term study of these patients is both interesting and exciting and should lead to a better understanding of the management of ocular hypertension.

British Journal of Ophthalmology, 1977, **61**, 668–674

Ocular hypertension—a long-term follow-up of treated and untreated patients

ROBERT DAVID, DESIREE G. LIVINGSTON, AND MAURICE H. LUNTZ
From the Department of Ophthalmology, University of the Witwatersrand and Johannesburg Teaching Hospitals, Johannesburg, South Africa

SUMMARY Sixty-one patients with ocular hypertension (117 eyes) were followed up for 1 to 11 years (average 40·7 months). Ten patients (12 eyes) developed visual field defects and optic disc lesions of glaucomatous type (10·2 %). Their average age was lower than the average of the sample, and the defect appeared between 1 and 5 years (average 41·3 months).

The risk of developing glaucoma was related to the level of the intraocular pressure. Of the 75 eyes with pressures between 21 and 25 mmHg only 2 developed glaucoma, of the 25 cases with pressures of 26 to 30 only 3, but 7 of the 17 eyes with pressures of 31 mmHg or more did so. Prophylactic cryosurgery was carried out where indicated by the presence of lattice retinal degeneration or holes before starting miotic therapy.

Fifty eyes were given antiglaucoma therapy and compared with 67 eyes not treated. Treatment did not prevent the development of glaucoma and did not seem to influence the course of the ocular hypertension. The response to treatment was also valueless in predicting future glaucoma. Two untreated patients with high pressures developed central vein occlusion. As no harmful effect of treatment could be detected in the 50 treated eyes, elderly patients (more than 70 years) with intraocular pressure higher than 26 mmHg in the presence of systemic vascular disease should have their intraocular pressure lowered if possible before the development of field defects. In those with intraocular pressure below 26 mmHg there is no advantage in prescribing treatment. In the range 26 to 30 mmHg it is our practice to treat elderly patients over the age of 70 years, while younger patients are treated only if their intraocular pressure exceeds 30 mmHg.

Screening programmes to detect raised intraocular pressure (IOP) are widely used because of increasing awareness of both ophthalmologists and the general population of the symptomless presentation and progression of chronic open-angle glaucoma. After careful examination of those with raised intraocular pressure an ever growing group of patients is emerging who, in spite of a raised intraocular pressure, show neither pathological cupping of the optic disc nor a glaucomatous visual field defect. These patients are labelled 'ocular hypertensives'.

The incidence of ocular hypertension (OHT) in the general population is variously reported as 1 % in the Oxford survey (Luntz *et al.*, 1963), 1·3 % in the Birmingham study (Walker, 1974), and 5 % in the Bedford survey (Perkins, 1973b). This is about five times higher than the incidence of glaucoma in the latter two studies (0·31 % in the Birmingham study and 0·93 % in the Bedford survey (Bankes *et al.*, 1968)). The incidence in a glaucoma clinic population is much higher—according to one report 11 % (Luntz, 1972).

Some authors believe that ocular hypertension represents a preglaucomatous stage (Richardson, 1972; and Goldmann, 1959). Others report on varying degrees of risk of patients with ocular hypertension for developing glaucoma. Graham (1968) and Armaly (1969) found it as low as 0·5 %, Linner and Stromberg (1967) 2 %, Perkins (1973a) 3·23 %, and Walker (1974) as high as 20 %. Kass *et al.* (1976) following up OHT eyes in patients with glaucoma in the second eye found 29 % to develop visual field defects.

These reports leave little doubt that patients with ocular hypertension run a higher risk of developing chronic glaucoma than the rest of the population in a similar age group. Nevertheless, only the

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minority of patients with ocular hypertension will develop glaucoma, but the exact parameters that would indicate that a patient with ocular hypertension will develop glaucoma are not known. In this context, for example, there are conflicting views about the effect of treating intraocular pressure—does this reduce the risk of progression to glaucoma or not?

The results are reported of a prospective study to determine: (1) The incidence for the development of glaucoma in a population with ocular hypertension carefully monitored for intraocular pressure, visual field changes, and the appearance of the optic disc. (2) The time interval between first diagnosing ocular hypertension and the development of glaucoma. (3) If treatment of the intraocular pressure would protect the eye from developing glaucoma when compared to those not having been treated. (4) Any side effects or complications of long-term treatment.

Definition of criteria

Patients attending our glaucoma clinics were diagnosed as OHT if: (1) The untreated intraocular pressure is found to be 21 mmHg or more on repeated measurements with the Goldmann applanation tonometer (Graham, 1972). The mean value of 3 pressures measured within the first few weeks of the patient's presenting to hospital is referred to in this paper as 'the mean initial intraocular pressure'. (2) The visual fields are normal when tested both with the Goldmann perimeter and the Bjerrum tangent screen. (3) The optic cup is separated from the edge of the disc by pink-coloured normal tissue (Drance, 1975). (4) There is no excavation of the disc margin by the optic cup. (5) The filtration angle is open.

Material and methods

A total of 61 patients (117 eyes) with ocular hypertension have been followed for 1 to 11 years. All the patients attend the glaucoma clinics at the Johannesburg General Hospital and at the St. John Eye Hospital, Baragwanath. Fifty-six patients had bilateral ocular hypertension, 3 others unilateral ocular hypertension, the other eye being normal, and 2 patients had ocular hypertension in an only eye, the fellow eye being blind from disease other than glaucoma.

After the diagnosis of ocular hypertension is made—on the criteria mentioned above—the patients are reassessed at intervals of 2 to 6 months; intraocular pressure is measured at every visit and the optic disc examined by uniocular and binocular fundoscopy. The visual fields are tested on every occasion with the Goldmann perimeter and once or twice a year with the Bjerrum tangent screen. For perimetry the 4eI and 3bIV targets on the Haag-Streit make of Goldmann perimeter were used in a dark room and standard background illumination. On the Bjerrum tangent screen the test was done at 1 m, with a 1 mm size white target. The Friedman analyser was used as a supplementary test to confirm paracentral scotomata when these appeared on one of the dynamic perimetries in a patient with previously normal fields.

The following field defects were considered significant: (1) Enlargement of the blind spot, particularly if this occurred in an upward or downward direction towards the Bjerrum area. (2) Paracentral scotomata in the Bjerrum area. (3) Typical arcuate scotoma. (4) Peripheral nasal scotomata in the 'nasal step' area. (5) Peripheral field loss, i.e., nasal step or altitudinal scotoma.

In all our cases the field defect could be correlated to a corresponding area of pathological cupping at the disc.

For some time tonographic studies and provocative tests were regularly performed, but they were abandoned when it was recognised that these have limited—if any—prognostic value, both from our own experience and that of others (Linner and Stromberg, 1964; Armaly, 1969; Graham, 1972; Kronfeld, 1975).

In 34 patients (67 eyes) we did not treat the raised intraocular pressure; the remaining 27 patients (50 eyes) were treated. The latter are patients with an initial intraocular pressure of at least 35 mmHg, ocular hypertension which is present in an only eye, and, thirdly, a randomly selected group of patients with intraocular pressure below 30 mmHg who were placed on treatment as part of this prospective study to evaluate the influence of treatment on the natural history of the condition.

The treatment is pilocarpine (2, 3, or 4%) 3 to 4 times daily, with adrenaline 2% twice daily added when necessary. A few patients are also on acetazolamide.

Before beginning treatment, however, all patients had their pupils dilated, and a careful search was made for equatorial lattice degeneration or holes in the retina. Peripheral retinal holes were found in 1 patient and these were closed by cryosurgery prior to the miotic treatment.

Results

There are 36 females and 25 males, and the average follow-up is 42·8 months. Of the 117 eyes 48 (41%) have been followed up for more than 42 months, 69 (59%) for more than 3 years, and 29 (25%) for more than 5 years (Fig. 1).

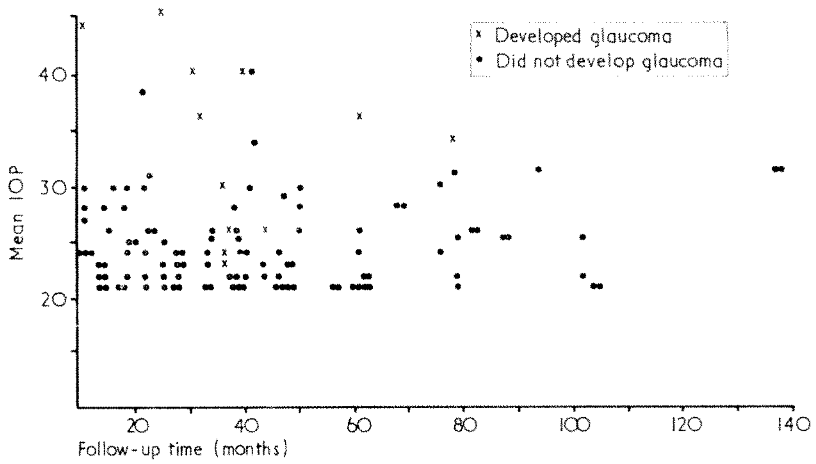

Fig. 1 *Mean intraocular pressure in patients who did and did not develop glaucoma*

In 75 eyes the means of their untreated intraocular pressure were between 21 and 25 mmHg, between 26 and 30 mmHg in 25 while 17 eyes had mean pressures higher than 31 mmHg measured on repeated occasions.

The age at which ocular hypertension was first diagnosed ranged from 36 to 83 years, 1 patient being 30 years of age. The mean was 61·2 years. The mean initial intraocular pressure and standard deviation were plotted for each age decade (Fig. 2). There appears to be no significant correlation in the mean intraocular pressure with advancing age.

Twelve eyes of 10 patients (10·2%) developed glaucoma, i.e., pathological cupping of their discs and glaucomatous field defect. Visual field defects appeared after 12 to 60 months of follow-up in 11 of the 12 eyes and in 1 after 79 months, the mean being 41·3 months. Fig. 1 illustrates the relationship between the mean of the initial 3 intraocular pressure readings in each eye (follow-up in months), indicating also those eyes which developed glaucoma.

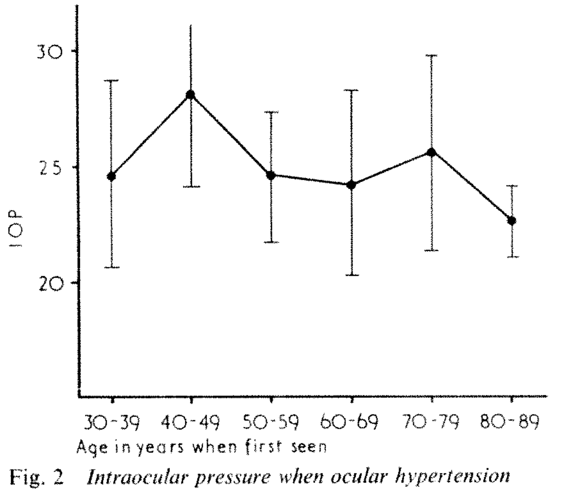

Fig. 2 *Intraocular pressure when ocular hypertension was first diagnosed*

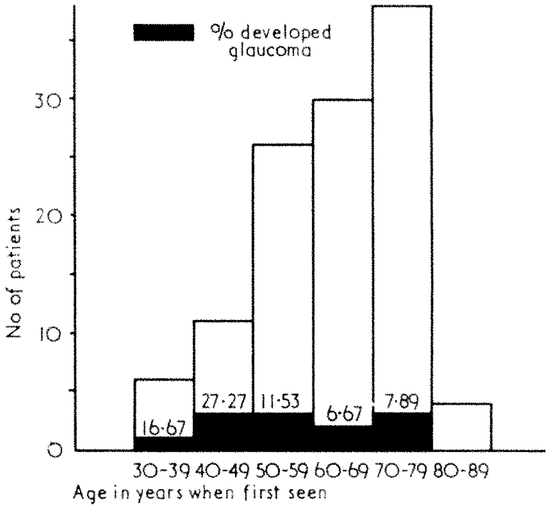

Fig. 3 *Development of glaucoma in relation to age*

The highest pressure levels were measured in the age group 40 to 49, and it is in this decade that the highest incidence of glaucoma occurred (27·3%) (Fig. 3). In Fig. 4 we present the distribution of intraocular pressure for each eye in the various age groups, indicating those eyes that developed glaucoma (12 eyes). Of these 12 eyes 50% presented with ocular hypertension in the age decades 40 to 59 and subsequently developed glaucoma.

A number of factors which influence progression

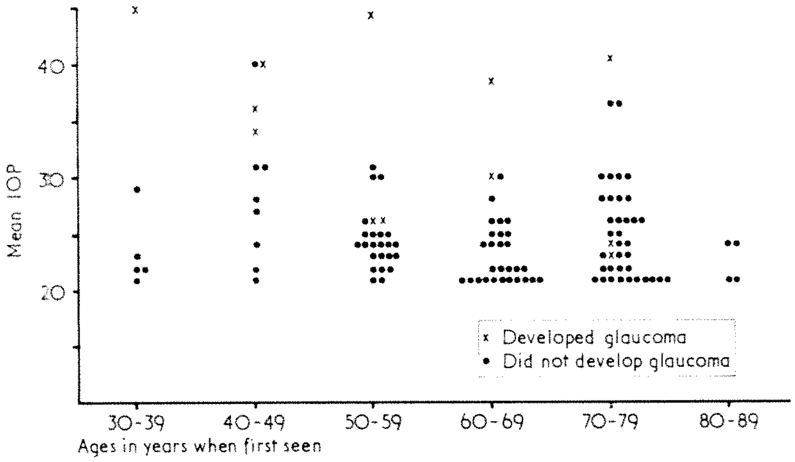

Fig. 4 *Distribution of mean intraocular pressures and presence or absence of glaucoma in relation to age*

of ocular hypertension to glaucoma were specifically looked at:

Concomitant systemic disease. Eleven patients are under medical care for systemic hypertension, 3 have well-controlled diabetes, 2 have chronic constrictive lung disease, and 1 is suffering from thyrotoxicosis. Only 1 of the hypertensive patients and 1 of the diabetics developed glaucoma.

A family history was noted in only 2 patients, but neither of these have so far developed glaucoma.

Age of onset. The 10 patients in our study who developed glaucoma were aged 36 to 75 with a mean age of 55·2 as compared with a mean of 62·1 in the total sample.

Cup/disc ratio. Of the 12 eyes that developed glaucoma only 9 had accurate cup/disc measurements documented. Four of these had a cup/disc ratio of less than 0·5, and 5 had cup/disc ratio of 0·5 (1), 0·7 (2), and 0·8 (2).

The level of the mean initial intraocular pressures (all patients initially untreated). Of the 12 eyes with ocular hypertension that developed glaucoma 7 had intraocular pressure of 31 mmHg or more, 3 between 26 and 30, and 2 of 21 to 25. In other words, of the 17 eyes with initial intraocular pressure of 31 mmHg or more 7 developed glaucoma (41·2%), 3 out of the 25 eyes with pressures between 26 and 30 mmHg (12%), and only 2 of the 75 eyes with pressures lower than 25 mmHg (2·7%) (Table 1).

EFFECT OF TREATMENT

Response of treatment. Fifty eyes with ocular hypertension (27 patients) are on antiglaucoma treatment, while the rest (34 patients, 67 eyes) receive no treatment. The response to treatment is considered 'good' when a drop of 11 mmHg or more was obtained, 'fair' when the decrease in the intraocular pressure was 6 to 10 mmHg, and 'poor' when the treatment reduced intraocular pressure by 5 mmHg or less.

Influence of treatment on development of glaucoma. Nine eyes (7 patients) developed glaucoma while on treatment. The response to treatment in the various pressure groups is shown in Table 2, and the outcome of treatment in all patients in Table 3. In Fig. 5 the relationship between mean intraocular pressure, length of follow-up, and the eyes which

Table 1 *The relationship between the level of mean initial intraocular pressure (IOP) and the development of glaucoma from ocular hypertension*

IOP	*Total eyes*	*Developed glaucoma*	%
21–25	75	2	2·7
26–30	25	3	12
31 or more	17	7	41·2
Total	117	12	10·3

Table 2 *Response to treatment*

	Eyes that did not develop glaucoma				*Eyes that did develop glaucoma*				
Initial mean IOP	*Response to treatment*				*Response to treatment*				*Total*
	Good	*Fair*	*Poor*	*Total*	*Good*	*Fair*	*Poor*	*Total*	
21–25	6	4	15	25	2	—	—	2	27
26–30	5	—	3	8	—	1	—	1	9
31	6	2	—	8	6	—	—	6	14
Total	17	6	18	41	8	1	—	9	50

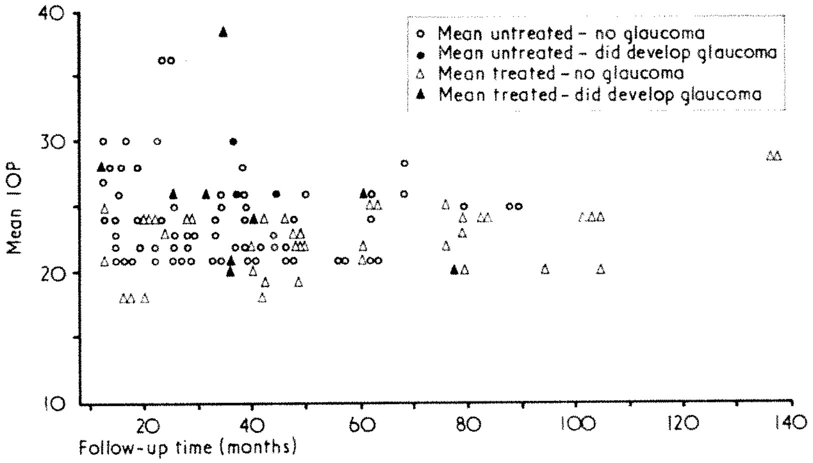

Fig. 5 *Relation between mean intraocular pressure, length of follow-up, and development of glaucoma*

developed glaucoma are plotted for both the untreated and treated eyes. In Fig. 5 mean intraocular pressure is the average of all intraocular pressures measured for each eye during the period of follow-up in both the treated and untreated groups.

Table 3 *Influence of treatment on the outcome of ocular hypertension*

IOP (Mean initial) (all patients initially untreated)	*Patients left untreated (eyes)*	*Developed glaucoma (eyes)*	*Patients subsequently treated (eyes)*	*Developed glaucoma (eyes)*
21–25	48	—	27	2
26–30	16	2	9	1
31 or more	3	1	14	6
Total	67	3	50	9

Treatment in relation to observed complications. Eight eyes (16%) showed a decrease of 2 lines or more in their visual acuity while on treatment owing to development of lens opacities, and 7 of these patients were over 70 years of age. In the untreated group 8 eyes (11·5%) showed increased lens opacities of similar degree, 5 of these in patients over 70. The difference is not significant.

During the follow-up period 3 patients developed occlusion of the central retinal vein. Two of these patients were not on antiglaucoma treatment, 1 is a hypertensive, both are over 70 years old, and their intraocular pressure was in the 26 to 30 mmHg range. The third patient is diabetic; the initial intraocular pressure was over 30 mmHg, and the patient responded well to pilocarpine.

Table 4 shows the earliest noted pathological

Table 4 *Earliest manifestations of glaucoma (12 eyes)*

Eye	*Disc*	*Bjerrum*	*Goldmann*
1	Upper temporal cupping	Inferiorly enlarged blind spot	Full
2	Inferotemporal cupping		Peripheral upper nasal scotoma
3	Inferotemporal cupping	Upper nasal scotoma	Full
4	Fundoscopically equivocal		Paracentral upper nasal scotoma
5	Fundoscopically equivocal		Paracentral upper nasal scotoma
6	Fundoscopically equivocal		Peripheral upper nasal scotoma
7	Fundoscopically equivocal		Peripheral lower nasal scotoma
8	Fundoscopically equivocal		Peripheral upper nasal scotoma
9	Inferotemporal cupping		Paracentral upper nasal scotoma
10	Inferotemporal cupping		Paracentral upper nasal scotoma
11	Temporal cupping		Paracentral nasal scotoma
12	Temporal cupping	Horizontally enlarged blind spot	—

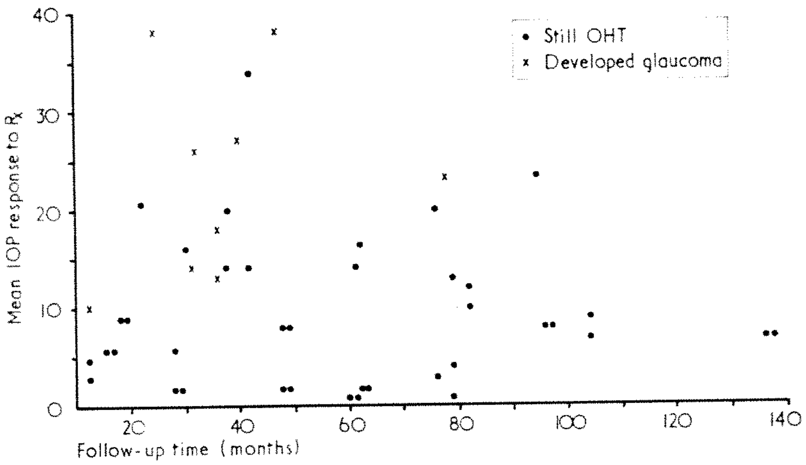

Fig. 6 *Response of intraocular pressure to treatment*

changes in the 12 eyes which developed glaucoma from ocular hypertension.

Discussion

Incidence of ocular hypertension progressing to glaucoma. The 10·2% of glaucoma developing from ocular hypertension found in our series is higher than figures quoted by other authors (Graham, 1968; Armaly, 1969; Linner and Stromberg, 1967; and Perkins, 1973a), but lower than the 20% found by Walker (1974).

The patients who developed glaucoma were slightly younger than the average age of the sample (mean age 55·2 years as compared with 62·1 years). This suggests that glaucoma occurring in a patient with ocular hypertension will become manifest early in the course of the ocular hypertension. In this series we noted that if glaucoma developed it did so usually within 5 years of the first presentation with ocular hypertension.

Earliest signs of glaucoma. In 7 cases the earliest sign of glaucoma was pathological cupping of the optic disc. This was confirmed by a matching defect on the Goldmann field (4 cases) or the Bjerrum screen (3 cases). The other 5 patients presented with nasal scotoma either peripheral (3) or paracentral (2) documented on the Goldmann perimeter (Table 4).

OTHER CLINICAL PARAMETERS

Initial intraocular pressure. The initial untreated intraocular pressure was the most consistent parameter for predicting the risk of glaucoma developing from ocular hypertension. As seen in Table 1, while the risk of glaucoma in patients with intraocular pressure of 25 mmHg or less was 2·7%, in the over 31 mmHg pressure group the risk was as high as 41·2%.

Treated eyes. The influence of treatment on the course of ocular hypertension is seen in Table 3 and Fig. 5. It is obvious that treatment did not prevent visual field loss, as more eyes on treatment developed glaucoma than those off treatment. Of 67 eyes not treated only 3 (4·5%) developed glaucoma, while of 50 treated eyes 9 (18%) developed glaucoma. The reason for this is that there are more patients with high intraocular pressure, who run the greatest risk of developing glaucoma in the group on treatment.

Furthermore from Table 3 it is clear that the same pattern of risk is seen in the eyes on or off treatment, i.e., those eyes in the highest range of intraocular pressure are at greater risk than those in the lower ranges (6 out of 14 treated eyes with intraocular pressure greater than 30 mmHg became glaucomatous).

While treatment did not prevent progression of ocular hypertension to glaucoma it did not, in this group of patients, do significant harm. The amount of cataract found in the treated group was similar to that in the untreated, and probably both were acceptable within the age-dependent incidence of cataract (Cinotti and Patti, 1968).

Response to treatment. The response of the intraocular pressure to treatment is recorded in Fig. 6 as the mean drop in intraocular pressure after treatment. Most of the eyes that developed glaucoma had responded well to treatment (a drop of 11 mmHg or more) but also had high initial intraocular pressure. On the other hand many of the eyes (about one-third) that did not develop glaucoma also responded well to treatment. Therefore, in reading the results documented in Fig. 6 the effect of the initially high intraocular pressure is probably more important in determining progression to glaucoma than is the response to treatment, but both factors appear to play a part.

The patients had their intraocular pressure monitored at 3-monthly intervals and were measured at different times during the day. The mean drop in intraocular pressure resulting from therapy in the treated group as a whole was 10·5 mmHg, the pressure dropping from a mean initial pressure of 31·6 mmHg to a mean pressure on treatment of 21·1 mmHg. In spite of this considerable drop in intraocular pressures these patients were not adequately protected from developing glaucoma, as 18% of them developed the disease. It also did not seem to postpone the onset of glaucoma, as glaucoma developed on average within 3½ years.

The patients on treatment were not rigorously monitored in the sense of having regular diurnal variations of intraocular pressure measured at weekly or 2-weekly intervals to ensure that intraocular pressure was maintained under 20 mmHg at all times. It is possible but by no means certain that had such a rigorous regimen of control been followed these patients would have been adequately protected.

Our conclusion therefore is that, if the decision is made to treat a patient with ocular hypertension, then the ophthalmologist is committed to instituting treatment with a rigorous system of intraocular pressure control, by means of regular weekly or even daily (if the patient can do it himself) diurnal measurement of pressure to ensure that the intraocular pressure is constantly less than 20 mmHg. If this is not done then the patient is not protected against glaucoma.

If the intraocular pressure is not constantly maintained below 20 mmHg, either the medication must be increased, with the added risk of intensive medication, or the surgeon might as well abandon therapy. If intensive medication does not maintain intraocular pressure below 20 mmHg at all times of the diurnal curve, then the question of surgery arises. In our view ocular hypertensive patients run less risk if therapy is abandoned (only 10% of our patients developed glaucoma over 6 years, i.e., a 1·7% annual risk) compared to the risk of surgery.

Three patients suffered a central vein occlusion during the follow-up period and deserve some attention. All had an intraocular pressure higher than 26 mmHg. Only 1 was on treatment at the time the occlusion occurred, and this patient was diabetic and had intraocular pressure readings of 36 mmHg prior to therapy. The other 2 received no treatment for their ocular hypertension, although 1 was hypertensive and on medical care.

As long-term pilocarpine treatment does not seem to be unduly harmful provided that degenerative retinal disease or retinal holes are treated prophylactically, it would seem reasonable that elderly patients (more than 70 years) with ocular hypertension and intraocular pressure measuring 26 mmHg or more should be treated in an attempt to improve perfusion at the optic head and to decrease the risk of vein occlusion. This is especially true if the patient has systemic vascular disease or is receiving antihypertensive drugs. On the other hand if the intraocular pressure does not respond to treatment with a fall of 5 mmHg or more, the treatment should be stopped.

Otherwise treatment seems to be unnecessary in ocular hypertension in which intraocular pressure without treatment is 30 mmHg or less, and can be postponed until frank glaucoma develops—if at all.

We are grateful to Mrs Ferelyth Douglas for her help in preparing the illustrations.

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Diathermo-trabeculotomy ab externo: indications and long-term results

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SUMMARY The authors present the results of 2 years' observation of 47 eyes operated with diathermo-trabeculotomy ab externo. This technique, based on a diathermic effect in association with trabeculotomy ab externo, allows an ample opening of Schlemm's canal and of the trabecular meshwork, with normalisation of intraocular pressure and outflow facility, for a period of up to 2 years, in open-angle and congenital glaucoma.

The theoretical basis of diathermo-trabeculotomy ab externo is the concept that the diathermic effect prevents or delays the normal processes of scar formation in the tissues. By applying this concept in the field of ocular microsurgery we have associated this effect of diathermy with the traditional operation of trabeculotomy so as to avoid closure of the surgical opening, which often reduces the effectiveness of the operation after an interval of time.

The problem has been solved by a trabeculotome suitably insulated except for the part which comes into contact with the canal wall on the trabecular meshwork side.

Methods and material

The technical data and the operating technique have been published in this journal (Maselli *et al.*, 1975).

With this technique we have operated on 47 eyes, 35 of which were affected with chronic simple glaucoma, 10 with congenital glaucoma, and 2 with closed-angle glaucoma.

Results

In all cases of chronic simple glaucoma we have obtained, with a single operation, normalisation of the intraocular pressure (IOP) and an improvement in the outflow facility.

Among the 10 cases of congenital glaucoma, 8 have subsequently shown normalisation of IOP and outflow facility. In 2 cases the success has been partial, with a reduction of IOP to between 23 and 26 mmHg, and an increase of the outflow facility, which although not completely normalised, was decidedly above the initial values and never below 0·10.

With this technique we have also operated on 2 cases of closed-angle glaucoma, both of which showed elevated IOP within 6 months of the operation (Table 1).

The results of periodic postoperative examinations after 6, 15 and 24 months are given in Tables 2, 3, and 4, showing the IOP, outflow facility, visual field, and visual acuity.

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Table 1 *Postoperative intraocular pressure (47 eyes)*

Type of glaucoma	*Cases*	*IOP≤22 mmHg*	*IOP>22 mmHg*
Open-angle	35	33	2
Congenital	10	8	2
Closed-angle	2	1	1

Table 2 *Intraocular pressure after 6 months (43 eyes)*

Type of glaucoma	*Cases*	*IOP≤22 mmHg*	*IOP>22 mmHg*
Open-angle	33	32	1
Congenital	10	8	2

Table 3 *Intraocular pressure after 15 months (32 eyes)*

Type of glaucoma	*Cases*	*IOP≤22 mmHg*	*IOP>22 mmHg*
Open-angle	22	22	0
Congenital	10	8	2

Table 4 *Intraocular pressure after 24 months (18 eyes)*

Type of glaucoma	*Cases*	*IOP≤22 mmHg*	*IOP>22 mmHg*
Open-angle	12	12	0
Congenital	6	6	0

Table 5 *Results more than 6 months after diathermo-trabeculotomy*

Type of glaucoma	*Cases*	*IOP (mmHg)*				*Failures (uncontrolled IOP)*	*Partial successes (IOP 23–26 mmHg)*	*Successes (IOP≤22 mmHg)*
		11–14	*15–18*	*19–22*	*23–26*			
Open-angle	33	2	24	6	1	—	1 (3·3%)	32 (96·7%)
Congenital	10	—	2	6	2	—	2 (20%)	8 (80%)
Closed-angle	2	—	—	—	2	2 (100%)	0	0

Discussion

From examination of these results the following conclusions may be drawn. The percentages of success after a period of 6 months differ according to the various types of glaucoma (Table 5). Diathermo-trabeculotomy undoubtedly achieves its best results in cases of chronic simple glaucoma. As regards congenital glaucoma, the percentage of successes is not inferior to that which many surgeons have obtained with trabeculotomy ab externo and with goniotomy (D'Ermo and Bonomi, 1973), and there were no complete failures.

Failure in the 2 cases of closed-angle glaucoma confirms the theroretical considerations which exclude trabeculotomy as an operation for such cases.

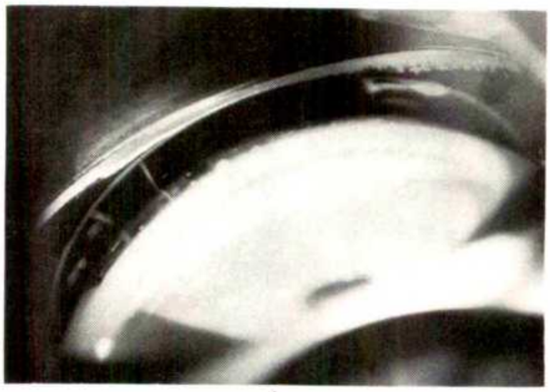
In conclusion, diathermo-trabeculotomy has proved harmless and without side effects, owing to the complete insulation of the probe. Sometimes at the moment of passing the current we have observed a slight retraction of the iris at its root owing to the diathermic effect; however, the pupil always becomes round and central again within 48 hours of the operation. In no case, even after a long period of time, have we noted the appearance of opacity of the lens.

The gonioscopic examination in the postoperative period has clearly shown, even in the cases controlled 2 years after the operation, an ample surgical opening of the angle, the edges of which show the signs of diathermy (Figs. 1 and 2).

The localisation of Schlemm's canal sometimes creates difficulty for the surgeon, but our experience leads us to think that, even when it is not absolutely certain that the probe is in the canal, the mere opening of the trabecular meshwork is sufficient to normalise the IOP.

Finally this method, in our opinion, overcomes the well-known limitations of trabeculotomy ab externo, eliminating the principal drawback of this technique, that is to say, the high incidence of closure of the surgical opening after a short time, especially in congenital glaucoma, where scar tissue formation is frequent.

Consequently, we consider diathermo-trabeculotomy ab externo a valid alternative to simple trabeculotomy and to the trabeculectomy of Cairns in open-angle glaucoma, and to goniotomy in congenital glaucoma, particularly in those cases where corneal oedema does not permit a good view of the angle.



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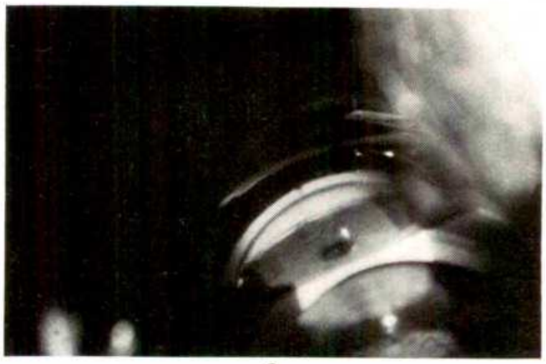

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Figs. 1 *and* 2 *Gonioscopic appearance 2 years after operation*

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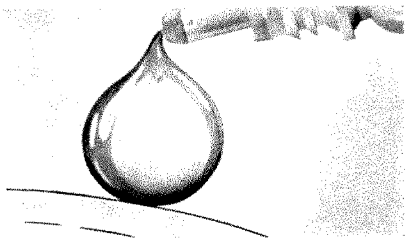

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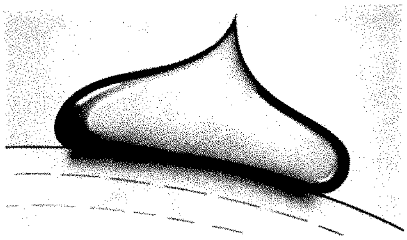

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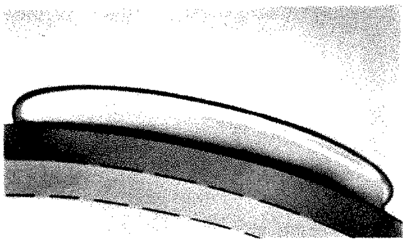

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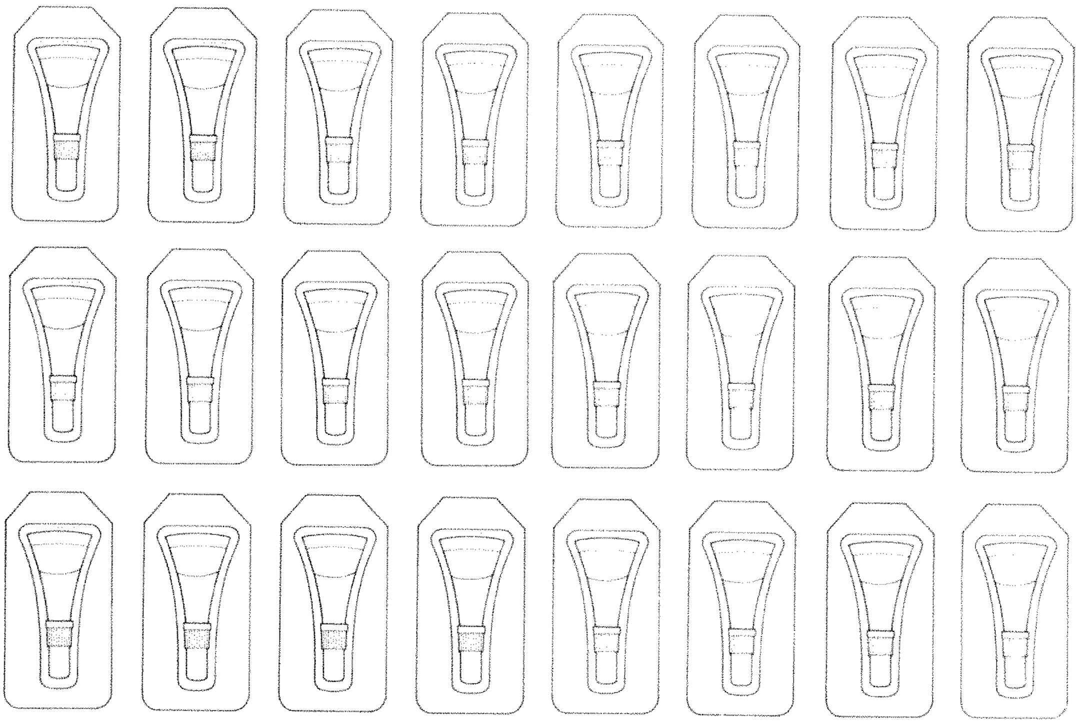

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British Journal of Ophthalmology, 1977, **61**, 677–682

External ocular motor palsies in ophthalmic zoster: a review

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SUMMARY Seventy-seven new patients suffering from ophthalmic zoster and a selected group of 69 old patients were carefully examined with regard to external ocular movements. An incidence of 31% of ocular pareses was found in the new patients, and 58 in all were analysed. We were surprised to find several of these were contralateral and bilateral palsies. 28% of the palsies were asymptomatic, due to diplopia being present only in extremes of gaze and the rapid development of suppression in the affected eye. The theories of aetiology of these pareses are discussed.

Herpes zoster ophthalmicus produces widely varying lesions of the eye in 50% of cases (Edgerton, 1945a) and rarely involves other parts of the central nervous system (Edgerton, 1945b; Walsh and Hoyt, 1969; Thomas and Howard, 1972; Marsh, 1976a). It is thought to arise by reactivation of varicella virus lying latent in the trigeminal ganglion after a prior attack of chicken pox (Garland, 1943; Hope-Simpson, 1965), the virus replicating and migrating peripherally to skin, orbit, and centrally to the brain stem (Godfredson, 1948; Esiri and Tomlinson, 1972).

The cranial involvement takes many forms. A meningoencephalitis may develop (Schiff and Brain, 1930; Krumholz and Luihan, 1945; Worster-Drought and Sargent, 1949; Appelbaum *et al.*, 1962; Rose *et al.*, 1964; Norris *et al.*, 1970). Contralateral hemiplegia occurs rarely, either in an isolated form (Baudouin and Lantvejoul, 1919; Rollett and Colrat, 1926; Biggart and Fisher, 1938; Hughes, 1951; Cope and Jones, 1954; Minton, 1956; Laws, 1960; Acers, 1964), or accompanied by hemianopia (Franceschetti *et al.*, 1955), aphasia and agraphia (Gordon and Tucker, 1945; Leonardi, 1949; Anastostopoulos *et al.*, 1958). Other cranial nerves may be implicated simultaneously. Optic neuritis has been well described (Duke-Elder, 1940; Edgerton, 1945c; Pemberton, 1964; Harrison, 1965; Ramsell, 1967). The VIIth nerve is occasionally involved (Hunt, 1909; Edgerton, 1945d), and a contralateral VIIth nerve paresis has been described in 1 case (Norris *et al.*, 1970). Third, IVth, and VIth nerve palsies occur more frequently (Edgerton, 1945e; Goldsmith, 1968), the IIIrd being the commonest (Kelly and Dulley, 1975). All 3 may be involved together as a total ophthalmoplegia and are usually accompanied by proptosis (Carmody, 1937; Edgerton, 1945f; Lister, 1948; Pincus, 1949; Von Siegert, 1964). Many series have been published giving the incidence of extraocular muscle palsies as 5% (Hybord, 1872; Flament and Bronner, 1974), 7% (Desirat, 1903; Worster-Drought, 1923), 10% (Nover, 1970), 12% (Rebattu *et al.*, 1933), 13% (Edgerton, 1945g), and 14% (Hunt, 1909).

In this paper we present our own series based on a large number of patients.

Patients

The patients included in this study were drawn from those attending the zoster division of the External Diseases Clinic at Moorfields Eye Hospital, City Road, London, over a 4-year period. All were carefully examined with special reference to severity of rash, degree of neuralgia, the presence of nasociliary or lid margin involvement, episcleritis/scleritis, keratitis, iritis, and iris atrophy, and any complaints of diplopia were noted. A special note was added on the sectoral distribution of the lesions. Corneal sensation was measured centrally and in the 4 outer quadrants with the aesthesiometer of Cochet and Bonnet. Special investigations included haemoglobin concentration, ESR, differential white count, blood film, plasma protein electrophoretic strip, blood sugar, liver function tests and chest *x*-ray.

Two of the authors examined in detail the ocular movements of all new patients passing through the clinic in an 8-month period (77 patients) and a

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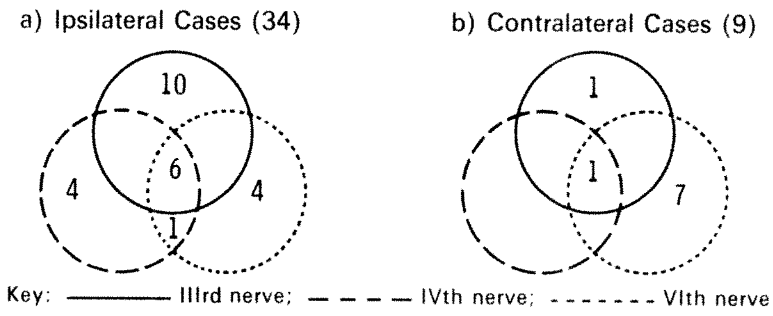
a) Ipsilateral Cases (34)
10
4
6
4
1
b) Contralateral Cases (9)
1
1
7
Key: ———— IIIrd nerve; — — — — IVth nerve; - - - - - - - VIth nerve

Fig. 1 *Distribution of nerve involvement in external ocular palsies*

selected group of old patients attending for follow-up (69 patients), many of whom had been previously diagnosed as having ocular palsies due to zoster. Tests were carried out at each attendance regardless of subjective symptoms and included cover test, ocular movements, convergence, assessment of binocular function, and Lees screen. A note was also made of the position of the upper lid margin.

Results

Twenty-two cases of paresis were found in the 77 new patients examined, giving an incidence of 29%. A total of 58 cases of external ocular muscle paresis were discovered among the new and old patients. Forty-two of them complained of diplopia, 32 constantly. Sixteen of the patients were asymptomatic, although 8 admitted to diplopia on testing in extremes of gaze. Careful analysis of the 58 pareses showed they tended to fall into 5 categories (Table 1). The different cranial nerves involved in the ipsilateral and contralateral groups are analysed in the Venn diagram (Fig. 1). The third category revealed slow recovery of the original ipsilateral paresis, and always a contralateral IIIrd nerve palsy superseded, although the same branch was not necessarily affected on each side (Table 2). A small percentage of cases had the same muscle paresis on each side from the beginning, but other underactions were present, usually on the side affected by the rash. Complete ophthalmoplegia was accompanied by proptosis in 3 of the 4 cases seen, and 1 of these in fact had bilateral ophthalmoplegia and proptosis.

Fig. 2 shows the age distribution of the patients with palsies, and it should be noted that the youngest was 46.

All the pareses were detected within the first week of the rash, although it was often difficult to examine

Table 1 *Laterality of external ocular palsy*

	Ipsilateral	*Contralateral*	*Ipsilateral becoming contralateral*	*Bilateral*	*Complete ophthalmoplegia*
No. of cases	34	9	6	5	4

Table 2 *Ipsilateral palsies becoming contralateral*

Cases	*Ipsilateral*		*Contralateral*
1 2	III	→	III
3	VI	→	III and IV
4 5	III and VI	→	III and VI
6	III, VI, and IV	→	III and VI

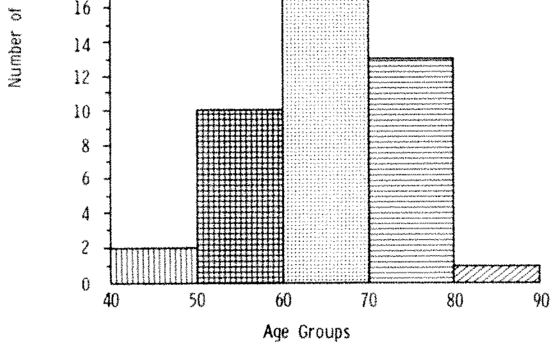

Fig. 2 *Histogram of age distribution in zoster*

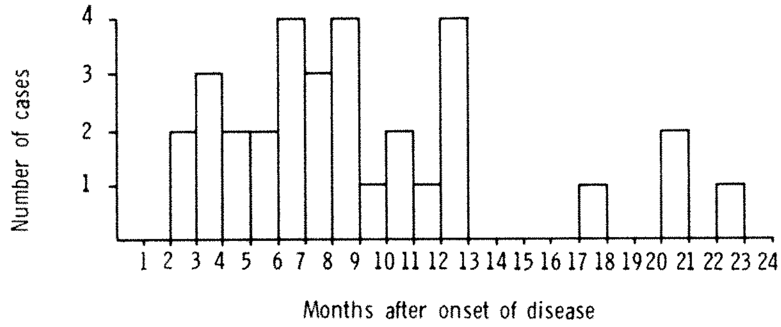

Fig. 3 *Histogram of duration of diplopia in ophthalmic zoster*

eye movements at this stage owing to the lid swelling and malaise of many of the patients.

Fig. 3 shows the duration of symptoms, and it is significant that there were only 3 cases lasting for more than 18 months. However, an orthoptic defect could always be found in all patients despite the excellent subjective recovery.

The incidence of other ocular complications of zoster in the ocular motor palsy group was compared with those occurring in a comparison group of 46 patients seen at the same time with no ocular motor defect. The results and statistical analyses are depicted in Table 3. There was no clear relationship between any of the sectoral lesions and a particular external ocular muscle underaction. Neither was there any significant correlation with the results of the special investigations.

Three patients had ipsilateral VIIth nerve paralysis without auricular involvement. A further 3 developed contralateral hemiplegia within 1 month of the onset of zoster, and a fourth developed an ipsilateral hemiplegia 2 years after the rash.

Table 3 *The association of external ocular palsies with other complications of ophthalmic zoster*

Complications of ophthalmic zoster	χ^2	*Probability*	*Remarks*
Severity of zoster	12·6	$P<0{\cdot}001$	Very highly significant
Neuralgia	5·9	$0{\cdot}05>P>0{\cdot}01$	Highly significant
Iritis	12·6	$P<0{\cdot}001$	Very highly significant
Iris atrophy	10·2	$0{\cdot}01>P>0{\cdot}001$	Highly significant
Sphincter damage	1·8	$0{\cdot}2>P>0{\cdot}1$	Non-significant
Corneal reflex	0·82	$0{\cdot}5>P>0{\cdot}3$	Non-significant
Corneal involvement	2·1	$0{\cdot}2>P>0{\cdot}1$	Non-significant
Episcleritis	0·2	$0{\cdot}7>P>0{\cdot}5$	Non-significant
Lid involvement	0·91	$0{\cdot}5>P>0{\cdot}3$	Non-significant

Discussion

We found external ocular motor palsies in ophthalmic zoster to be more common than previously indicated. This was probably related to the detailed examination of eye movements in all patients. 28% were asymptomatic owing to the diplopia being present only in extremes of gaze, poor sight in the affected eye, or to the development of suppression at a late age. Recovery was excellent despite the fact that an objective defect could always be found on orthoptic examination. The presence of a squint was significantly associated with the severity of the rash and the later occurrence of severe neuralgia, iritis, and iris atrophy, whereas episcleritis, and corneal and lid involvement were of no greater frequency. No case was seen under the age of 40. Surprisingly we found some of the palsies to be bilateral and on the side opposite to the skin lesions.

PATHOGENESIS

To try to understand the cause of bilaterality of some of the palsies and their relationship to other complications of zoster it is necessary to consider the pathogenesis of the lesions.

Three pathogenic mechanisms should be considered for mediating neural damage in zoster. The first is a direct cytopathic effect from the virus itself on the surrounding neural tissue (Cope and Jones, 1954). The second is an allergic response of the central nervous system to the virus, which is not primarily vascular (Krumholz and Luihan, 1945; Appelbaum *et al.*, 1962; Rose *et al.*, 1964). The third attributes it to an occlusive vasculitis induced by the virus (Gordon and Tucker, 1945; Feyrter, 1954; Anastostopoulos *et al.*, 1958; Wray, 1972). A fourth theory (for which there is little evidence) suggests the varicella/zoster virus activates another latent neuropathic virus within the brain (Appelbaum *et al.*, 1962).

Virus may reach the brain in several ways and there cause direct cytopathic or allergic damage to the nervous tissue. The first is a retrograde spread of virus from the trigeminal ganglion to the Vth nerve nucleus. Here it reaches other cranial nerve nuclei, either by axonal spread along established interconnections (Biggart and Fisher, 1938; Godfredson, 1948; Goodbody, 1953), or by random spread (Cope and Jones, 1954; Acers, 1964). The former pathway could be along the proprioceptive neurones of the oculomotor muscles in the Vth nerve (Denny-Brown *et al.*, 1944). Alternatively, virus may reach the brain by means of a basal meningoencephalitis, which is well described in the literature (Schiff and Brain, 1930; Wynne Parry and Laszlo, 1943; Gordon and Tucker, 1945; Godfredson, 1948; Hughes, 1951; Norris *et al.*, 1970). The area chiefly involved is thought to be the pontine region (Worster-Drought, 1923). Many features can be attributed to this: headache, general malaise, pyrexia, bilaterality of lesions, multiple cranial nerve palsies, hemiplegia, CSF findings, and the rare cases of cranial nerve lesions secondary to a remote primary zoster lesion (Thomas and Howard, 1972; Keane, 1975). Against this theory is the delayed occurrence of many of the cranial nerve lesions, the lack of symptoms and signs of encephalitis in many of the patients, and the rarity of bilateral lesions other than oculomotor palsies. Thirdly, a separate cranial motor neuritis may occur simultaneously with the trigeminal lesion, presumably also owing to the presence of latent virus activated by the same unknown stimuli. This could be a satisfactory answer for contralateral palsies and the occurrence of lesions at a different level from the primary rash (Denny-Brown *et al.*, 1944; Keane, 1975). However, it is somewhat unsatisfactory to postulate 2 distinct lesions and could not adequately explain the association of squints with other ocular complications of zoster.

The last pathogenic mechanism to be considered is that of occlusive vasculitis. Various sites have been prosposed. The earliest suggestion was that of the muscle cone and orbit with accompanying myositis, perineuritis, and thrombosis (Wyss, 1871; Abadie, 1898; Aubineau, 1914–15; Kreibig, 1938; Von Siegert, 1964). While this would be in keeping with the picture seen in total ophthalmoplegia with proptosis, iritis, and iris atrophy, it does not explain the isolated and contralateral ocular palsies we have seen or the rarer cases of contralateral hemiplegia.

The second site to be described was the cavernous sinus and orbit apex with involvement of the adjacent IIIrd, IVth, and VIth nerves (Rebattu *et al.*, 1933; Edgerton, 1945g; Franceschetti *et al.*, 1955; Walsh and Hoyt, 1969; Scheie, 1970). The difficulty here is to account for hemiplegias and the bilaterality of lesions, although it is true that the cavernous sinuses of both sides intercommunicate freely. The origins of the middle cerebral and ophthalmic arteries are here, and an ascending vasculitis may spread along these, with accompanying thrombosis (Gordon and Tucker, 1945; Anastostopoulos *et al.*, 1958). This may be mediated by a granulomatous angiitis induced by the varicella/zoster virus, involving the carotid artery, ipsilateral to the involved eye and segmental (Rosenblum and Hadfield, 1972; Victor and Green, 1976). In favour of this theory is the delayed onset of contralateral hemiplegias, hemianopias, and aphasias secondary to damage in the region of the internal capsule, and the occurrence of ischaemic optic neuritis and iritis. But it is a rather unsatisfactory mechanism for evoking contralateral ocular palsies.

A third site of vasculitis in the brain stem has been described pathologically by Feyrter (1954). This would, of course, account for ipsilateral palsies, contralateral hemiplegias (from involvement of the corticospinal tract), and lesions of adjacent cranial nerve nuclei. A spillover of the vasculitis just the other side of the midline could give rise to the contralateral ocular palsies.

It is possible, of course, that the palsies are of a mixed aetiology and that all the mechanisms and sites mentioned are involved.

TREATMENT

In view of the satisfactory recovery without treatment in most cases the question arises, Is any necessary? The minority that suffer very troublesome diplopia may need temporary occlusions.

An overall therapeutic solution to zoster must include an effective, non-toxic, systemic antiviral agent which crosses the blood brain barrier. If given at the very onset of the disease it would prevent both the direct and allergic cytopathic effect of the virus on neural tissue and prevent the initiation of a seondary vasculitis by destroying the virus at an early stage. However, a problem will still exist if cases present later on when these changes have been initiated, especially the vasculitis. It would seem logical to use systemic steroid in cases of occlusive vasculitis, and it is almost certain that total ophthalmoplegia with proptosis and ischaemic papillitis comes into this category (Marsh, 1976b).

It is quite clear that much work needs to be done on the pathogenesis of zoster and its complications. The disease is still a great mystery and despite its clearly proved association with varicella virus the theory of latency is not proved. The connections between the virus and lesions seen are also not understood. Neither is it known whether continuing presence of virus is necessary for the production of chronic lesions. There are many difficulties in clarifying these issues. No animal model exists for zoster, and there is a great problem in obtaining postmortem information on well-documented patients with zoster, especially in processing material for immediate histological, virological, and immunological checking. It is to be hoped that advances in these techniques will provide the therapist with the information he needs for the effective handling of this disabling disease.

We thank Professor Barrie Jones and Mr Alan Bird for their encouragement, Mr R. Fisher for his help with the statistics, and Mrs Jane Field for secretarial assistance.

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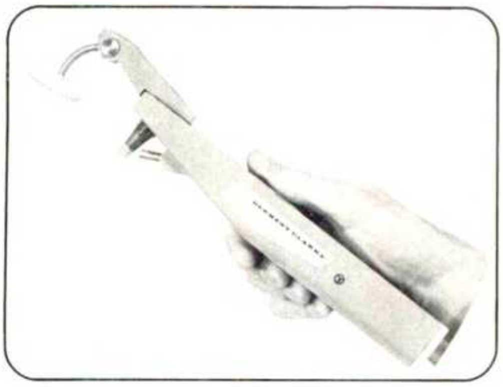

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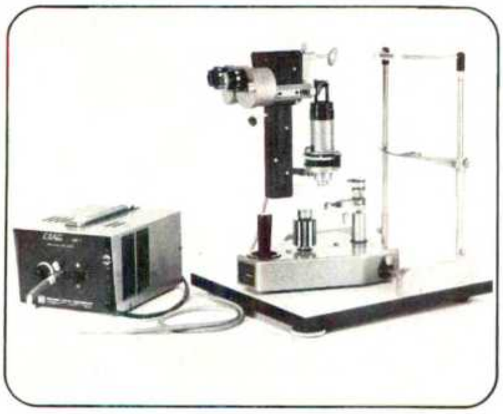

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Structural alterations of extraocular muscle associated with Apert's syndrome

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SUMMARY An inferior oblique muscle from a patient with Apert's syndrome was examined by light and electron microscopy. Alterations in the muscle fibres, the myoneural junctions, and intramuscular nerves were observed. These data are not compatible with the widespread notion that motility disturbances in this syndrome are solely due to mechanical limitations.

Apert's disease, or acrocephalosyndactyly (Apert, 1906), consists of oxycephaly (tower skull), exophthalmos, strabismus, antimongoloid fissures, maxillary hypoplasia, optic atrophy, and syndactyly (fusion of fingers 2 to 4). Ocular motility disturbances occur frequently in Apert's disease. It has been reported that at least 45 to 78% of patients seen with Apert's and Crouzon's diseases, both craniofacial dysostosis, have strabismus (Davis, 1925; Laitinen *et al.*, 1956). Overacting inferior oblique muscles and slight underaction of superior oblique muscles occurred frequently, It has been suggested (Lloyd, 1975; Miller and Folk, 1975) that these motility anomalies result from mechanical limitations of the globe which are secondary to the bony malformation of the orbit. In the present investigation, the first to directly examine the structure of extraocular muscle associated with Apert's syndrome, light and electron microscopic evidence is indicative of morphological abnormality.

Case report

The patient was a 13-year-old girl who had oxycephaly resulting from complete closure of the coronal sutures, shallow orbits, bilateral exophthalmos (Fig. 1), and syndactyly of the hands (Fig. 2) and feet. Consequently, she had a craniotomy to open the coronal sutures, and a follow-up examination showed normal motor progression, and good preservation of vision, with normal speech and intelligence. Over the years various surgical procedures had been performed to correct the physical deformities typical of Apert's syndrome—cleft palate, bifid uvula, and fusion of fingers.

OCULAR EXAMINATION

Cycloplegic refraction of the OD was +2·00 −0·25 × 90 and OS +2·25 sphere with visual acuity OD 20/40 and OS 20/30. Two years later examination showed a corrected vision of 20/25 OU. The patient had antimongoloid fissures with shallow orbits and prominent globes which measured at base 110 by exophthalmometer OD 20 mm and OS 19 mm. Further examination showed an interpupillary distance of 70·5 mm with an intercanthal distance of 39 mm. No nystagmus was evident. The

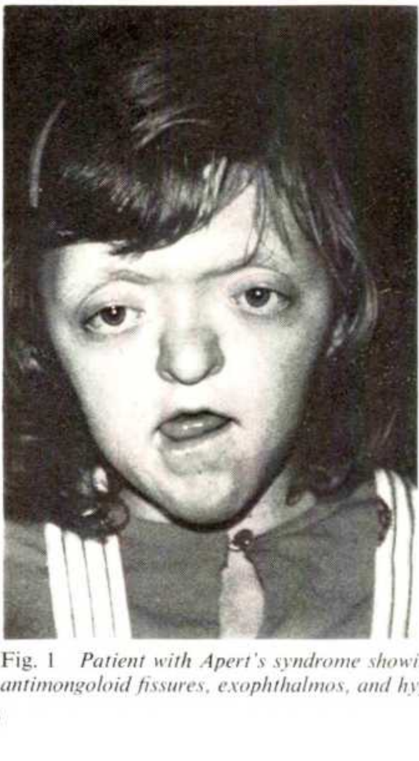

Fig. 1 *Patient with Apert's syndrome showing antimongoloid fissures, exophthalmos, and hypertelorism*

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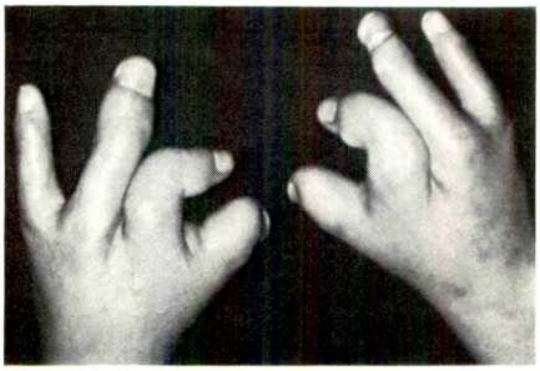

Fig. 2 *Syndactyly of fingers*

NPC was 40 mm. The anterior segment was unremarkable except for bilateral transillumination of the iris base. In addition it was noted in both eyes that the lens and vitreous were normal. Except for a suggestion of pallor of the right disc temporally, the optic nerves and blood vessels were normal. There were good foveal reflexes in both eyes, with decrease in the retinal pigmentation, which allowed for increased visibility of the underlying choroidal vessels anterior to the equator in the superior temporal and inferior nasal quadrants.

A 'V' pattern esotropia was present. On upward gaze there was an ET 25, RHT 14, and on downward gaze an ET 40, RHT 14 for distance and near. The patient had bilateral elevation in adduction, with overacting inferior obliques OU and underacting superior obliques OU. There was also decreased abduction OU with 3 mm of bared sclera. Sensory evaluation showed alternating suppression. Surgery for correction of strabismus was performed, which was 4 mm recession of left medial rectus, 8 mm recession of left lateral rectus, as well as bilateral inferior oblique disinsertions.

Laboratory tests: ERG, EOG, serum tyrosine, and phenylalanine levels and chromosome studies were all normal.

Materials and methods

The right inferior oblique was completely disinserted, and a segment of approximately 8 mm was taken from its belly portion and initially fixed in 1% paraformaldehyde/1% glutaraldehyde in phosphate buffer for 4 hours, then transferred to 4% glutaraldehyde overnight. The muscle segment was postfixed in 1% osmium tetroxide, dehydrated in graded alcohols, and embedded whole in Epon 812. The embedded muscle segment was serially sectioned at 15 μm by steel knife on a sliding microtome. These thick sections were cleared for light microscopy by curing a layer of Epon on to them within a sandwich of polystyrene film (Davidowitz *et al.*, 1976). The complete muscle biopsy could thus be initially surveyed by phase contrast for the detection of disrupted fibres and with particular emphasis on locating the neuromuscular junctions. Sections of interest were freed from the plastic sandwich and remounted for further 1 μm and ultrathin sectioning.

Results

LIGHT MICROSCOPY

Scattered among the predominantly normal-appearing fibres were cells in varying stages of degeneration (Fig. 3). Many fibres were enlarged and hyalinised. These and other cells frequently contained vacuolated regions and showed loss of myofibrillar organisation. Inflammatory infiltrates and lymphocytic collections were not observed.

ELECTRON MICROSCOPY

The hyalinised fibres typically contained large clusters of mitochondria and showed loss of myofibrillar organisation (Fig. 4). The mitochondria in such clusters often appeared swollen, disrupted, and vacuolated; their cristae showed fragmentation.

Other fibres showed varying degrees of vacuolar aggregations. Such vacuoles most probably represented swollen sarcoplasmic reticulum and/or resulted from mitochondrial breakdown. In Fig. 5 a vacuolar aggregate is seen in a muscle fibre showing minor myofibrillar disruption. In an advanced stage of cellular degeneration the vacuolar aggregates become increased in amount and there is loss of myofibrillar organisation (Fig. 6). Quite often, necrotic myofibrils were fused into an amorphous mass, which form electron-dense serpentine strands.

Various nuclear abnormalities were seen. They included highly involuted configurations, often with various pseudoinclusions (Fig. 7), as well as pyknotic nuclei.

Subsarcolemmal inclusions were frequently observed. One type was composed of finely granular, particulate matter, which formed regular clustering about foci which tend to be spaced at approximately 1200–1400 Å (Fig. 8). Their electron density varied from light (Fig. 8) to moderate (Fig. 9). A second type of inclusion appears to be a Hirano body (Fig. 10).

Neuromuscular junctions were seen on apparently normal and disrupted fibres. In some cases the axonal terminals appeared highly pyknotic (Fig. 11). These axonal terminals occasionally showed some loss of their axolemma.

The intramuscular nerves at times showed alterations. In many cases such nerve twigs contained

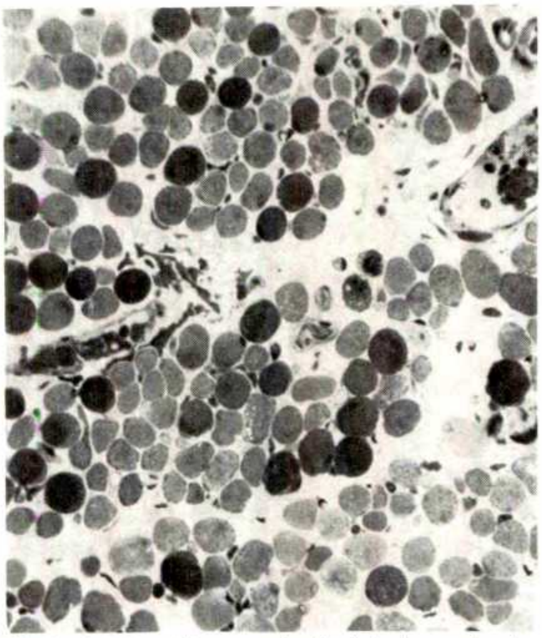

Fig. 3 *Inferior oblique muscle. Hyalinised, vacuolated, and necrotic fibres are seen (methylene blue,* × 260)

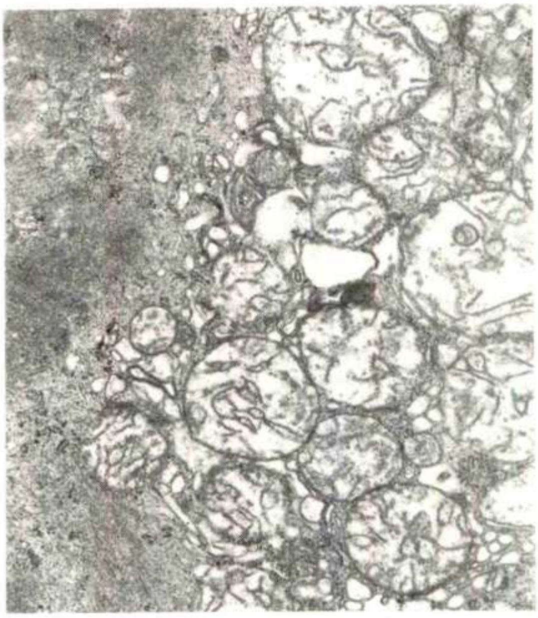

Fig. 4 *Marked clustering of mitrochondria, which are in various stages of disruption. The myofibrillar organisation is indistinct* (× 15 000)

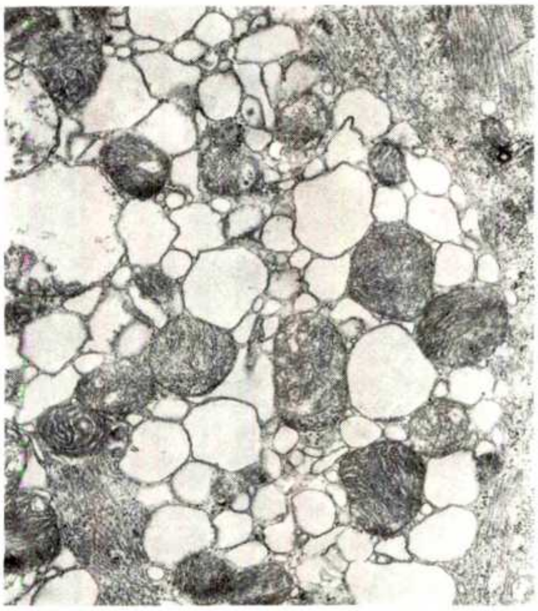

Fig. 5 *A large vacuolar aggregate, consisting presumably of dilated sarcoplasmic reticulum components and mitochondria which have degenerated* (× 15 000)

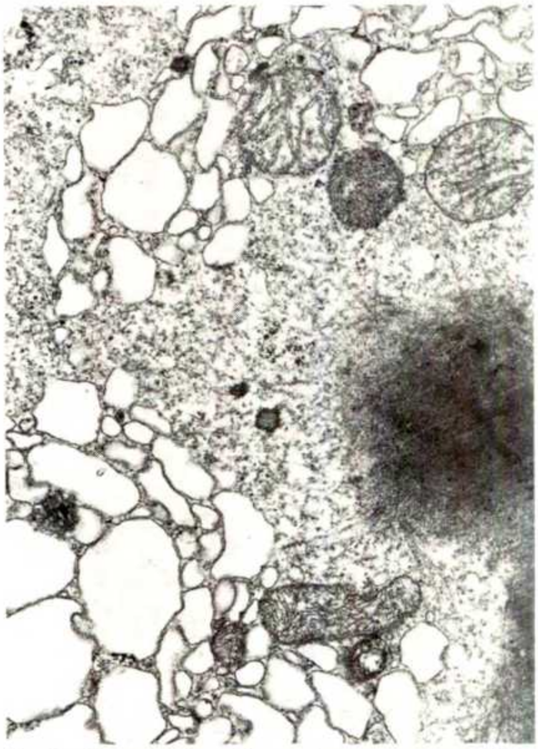

Fig. 6 *Necrotic fibre with vacuolar aggregates and loss of myofibrillar material* (× 15 000)

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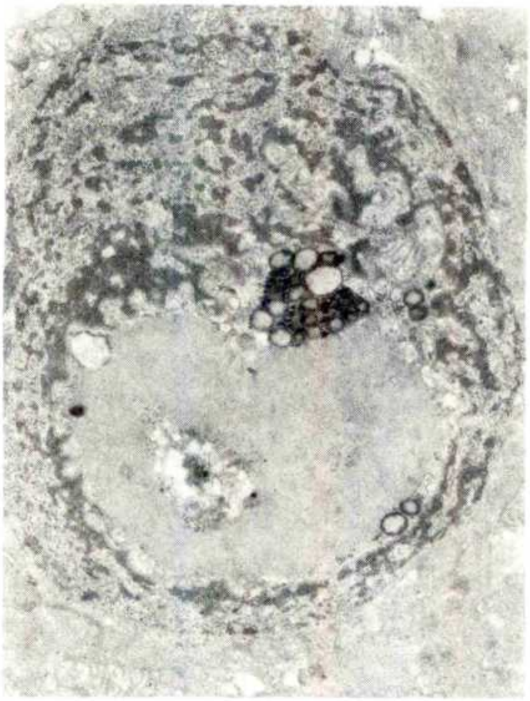

Fig. 7 *A large nuclear pseudoinclusion containing an inclusion body and lipofuscin material* (× 11 000)

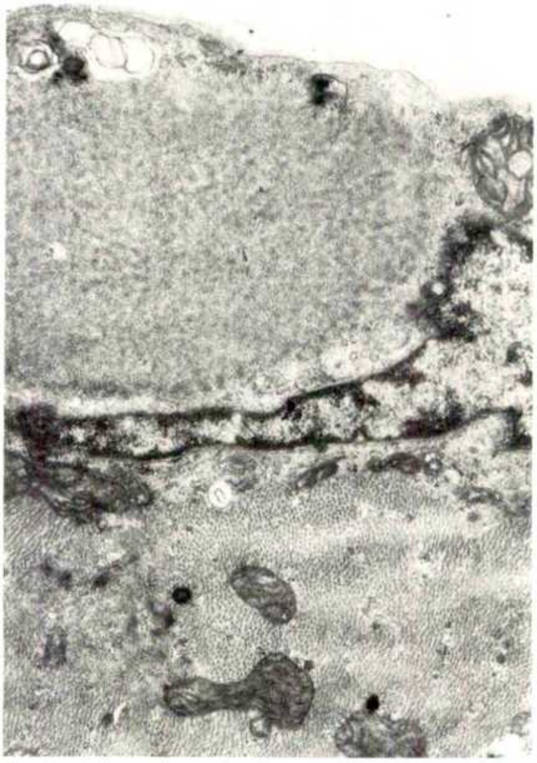

Fig. 8 *Subsarcolemmal inclusion body, non-membrane bound, composed of finely granular particulate material in an apparently normal muscle fibre* (× 15 000)

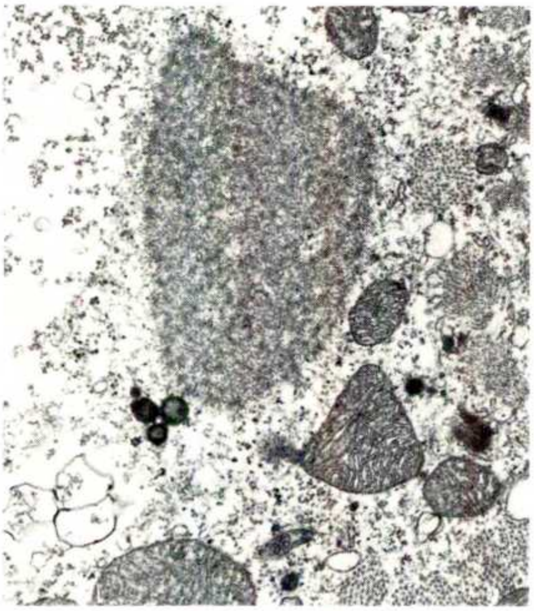

Fig. 9 *Subsarcolemmal inclusion body, non-membrane bound, and moderate electron density in a disrupted muscle fibre* (× 15 000)

laminated structures (Luse bodies) characterised by a definite periodicity. Such structures appeared to arise from or to be in close association with the basement membrane of the Schwann cell (Fig. 12). Schwann cell inclusions were also seen (Fig. 13). These appeared similar to the π granule of Reich. The axons within the nerve twigs occasionally showed significant myelin degeneration (Fig. 14).

Discussion

The high frequency of various alterations in muscle cell structure observed here strongly suggests a pathological state.

In the present study mitochondrial aggregates were observed in the fibres of both the orbital and the global regions. In a recent study of overacting inferior oblique from patients with various types of strabismus by Mukuno *et al.* (1976) myopathic alterations were observed, prominent among which were central cores of closely packed aggregates of mitochondria. These were mostly seen in small-diameter fibres on the orbital surface and were rare

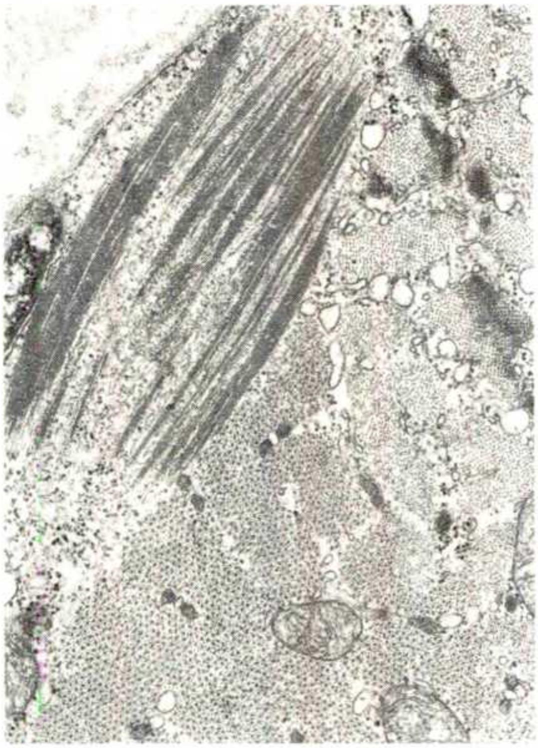

Fig. 10 *A subsarcolemmal Hirano body inclusion* (× 21 000)

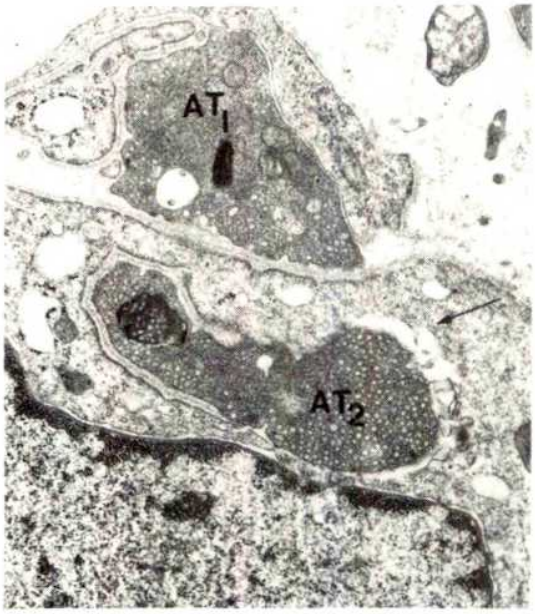

Fig. 11 *Motor endplate showing two axonal terminals (AT_1 and AT_2) which appear pyknotic. One axonal terminal (AT_2) shows a focal loss of its axolemma; the subjunctional region shows some degeneration* (arrow) (× 15 000)

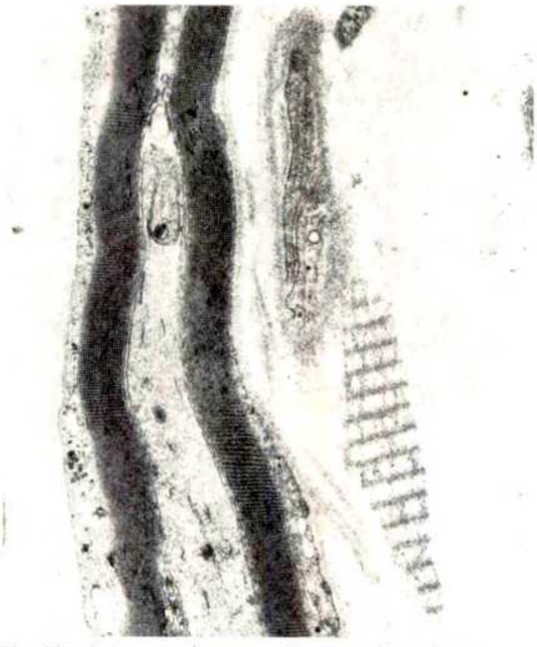

Fig. 12 *Intramuscular nerve showing a Luse body (elongated laminated structure) apparently attached to the basement membrane of the Schwann cell* (× 21 000)

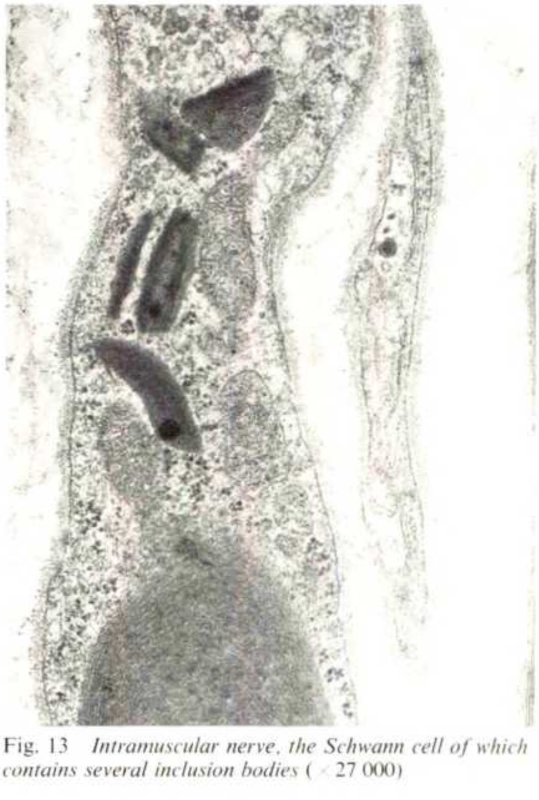

Fig. 13 *Intramuscular nerve, the Schwann cell of which contains several inclusion bodies* (× 27 000)

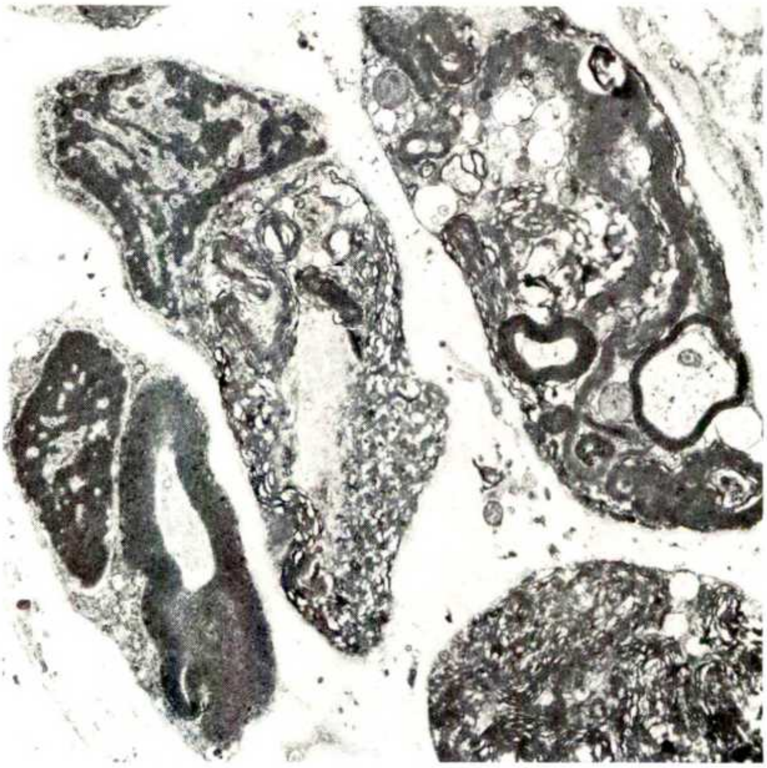

Fig. 14 *Intramuscular nerve showing myelin degeneration* (× 13 000)

in the global region. Mitochondrial abnormalities, such as aggregation, distension, vacuolation, and fragmentation, have been described in both myopathic and neurogenic diseases with altered ocular movements (Sakimoto, 1970; Adachi *et al.*, 1973).

Subsarcolemmal inclusions of finely granular structures and Hirano bodies were frequently observed in this study. Comparable granular structures have been previously described in extraocular muscle from patients with myotonic dystrophy (Culebras and Merk, 1975), from ageing individuals (Miller, 1975), as well as other neuromuscular disorders (Mair and Tome, 1972). Hirano bodies have been seen in myasthenic extraocular muscle (Sakimoto, 1968) and in a clinically overacting inferior oblique from a patient with exotropia (Martinez and McNeer, 1976). They also occur in cortical neurons showing neurofibrillary degeneration and granulovacuolar bodies in patients with Guam amyotrophic lateral sclerosis-parkinsonism-dementia complex (Hirano, 1965).

Alterations of the neural apparatus were less prominent. These included occasional disruption of neuromuscular junctions, axonal degeneration, and the presence of Luse bodies, and Schwann cell inclusions which were similar to the π granules of Reich. Luse bodies have been reported in pathologic extraocular muscle (Martinez and McNeer, 1976), as well as in neurogenic tumours (Friedmann *et al.*, 1965). The π granules of Reich have been described in nerves of patients with various neuromuscular disorders (Evans *et al.*, 1965) and in nerves from patients with hypothyroid neuropathy (Dyck and Lambert, 1970).

It thus seems likely that, at least in this case of Apert's syndrome, the motility disturbance may in part be related to abnormality of the extraocular muscles themselves rather than be due to mechanical factors alone.

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Diagnosis and measurement of cyclodeviation

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SUMMARY A simple, convenient, and accurate method of detecting and measuring even the smallest degree of cyclodeviation with the help of two special major amblyoscope slides is described. Routine use of these slides in the investigation of all paralytic squints to detect and measure cyclodeviation is suggested. This will prove useful in the correct diagnosis and in the adequate management of a case of cyclovertical muscle palsy.

The importance of the detection and measurement of cyclodeviation in all cases of paralytic squint is being increasingly realised, but it has not yet been a routine practice with all orthoptists and strabismologists because of the absence of a handy and at the same time accurate method of testing. Of the various methods commonly employed to detect cyclodeviation the Maddox double prism test and the Bielschowsky apparatus cannot measure it. The Maddox wing measures cyclodeviation only for near vision. The Maddox rod placed in a trial frame is often used to measure the defect at different distances and in different gaze positions, but a slight tilt of the frame or a slight malpositioning of the rod in the frame affects the measurement. We have also found the trial frame limits the extent of excursion of the eyes from primary to other gaze positions and thereby limits the usefulness of the method in cases of mild paresis of a cyclovertical muscle. Moreover, in this method the extent of excursion of the eyes from the primary positions cannot be measured, and therefore identical testing condition cannot be provided in subsequent follow-ups, which is essential for comparing the findings in order to assess progress.

The after-image method as described by Sood and Sen (1970) is useful, but some patients find it difficult to appreciate the tilt of the after-image, especially when it is slight. This method is also less convenient for measuring the deviation in the 9 cardinal positions of gaze, as the after-image often does not last long enough and has to be produced several times. Since a major amblyoscope is used in most orthoptic centres to measure horizontal and vertical deviation, it is quite convenient to measure the cyclodeviation also at the same time. A major amblyoscope also permits measurement of the extent of excursion of the eyes from the primary position. However, the SMP slides generally used for this purpose do not permit precise measurement, and therefore special slides are needed.

The purpose of this communication is to describe two special slides that we have been using with the Clement Clarke major amblyoscope for the last year to measure cyclodeviation routinely in all cases of cyclovertical muscle palsy. These slides permit more accurate measurement of the defect than those (Nos. A17 and 18) introduced by Clement Clarke some years ago. Another added advantage of our slides is that the patient reads off the measurement directly from the slides.

Description of slides

Slide 1. This is similar to slide A of the after-image method (Sood and Sen, 1970) with some modifications. It consists essentially of a black circle on a white background. The circumference is marked in degrees, and the markings are extended at 30° intervals towards the centre like the spokes of a wheel. Each small division represents 2°. There is a small circle in the centre which acts as a target (Fig. 1).

Slide 2. This consists of a thin black cross with a black dot in the intersection which also acts as a target (Fig. 2).

The slides have been so designed that when both the pictures are superimposed the black dot in the intersection of the cross coincides exactly with the small circle in the centre of the large circle, and the vertical and horizontal lines of the cross coincide with the 90° to 90° and 180° to 180° axes of the large circle respectively and extend a little distance

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beyond the circumference of the circle in both the axes.

Method of testing

After the determination of the refractive error and investigation of the type of squint and binocular functions the patient is placed in front of the major amblyoscope. Slide 1 is placed upright before the healthy eye and slide 2 is likewise placed before the affected eye. The arms of the major amblyoscope are so set that the black dot in the intersection of the cross coincides exactly with the small circle in the centre of the large circle. The patient is now asked to describe the position of the vertical line (or the horizontal line) in relation to the markings on the circumference of the large circle. If, for example, the vertical line points to 90° to 90° there is no cyclodeviation. If the upper end of the vertical line deviates nasally, excyclodeviation is present, and if the upper end deviates temporally then incyclodeviation is present. The degree of deviation can be read off by the patient directly from the markings on the circumference of the large circle. The reading can also be cross-checked by rotating the slide 2 in order to bring the tilted line back to coincide 90° to 90° axis of slide 1; the required degree of rotation of the slide read off by the investigator from a scale provided in the major amblyoscope is the measurement of cyclodeviation. The cyclodeviation is measured in 9 cardinal positions of gaze, the excursion of the eye from the primary position being kept constant so that the readings obtained in all follow-up tests are comparable.

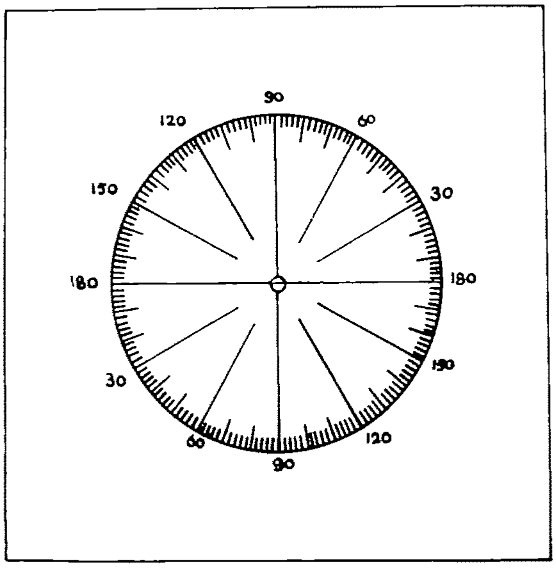

Fig. 1 *Slide 1*

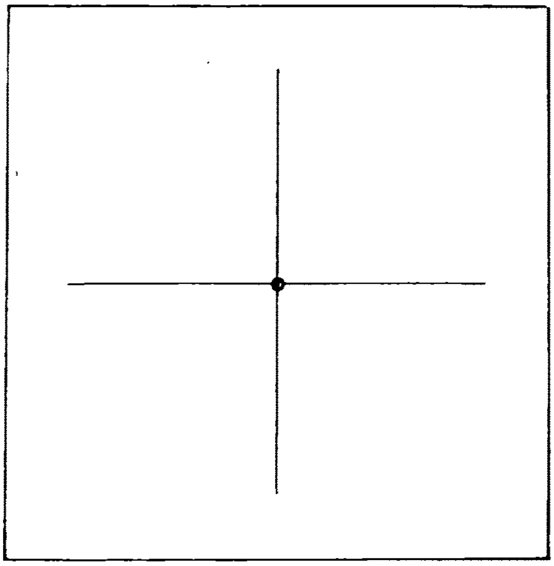

Fig. 2 *Slide 2*

Discussion

Measurements of cyclodeviation are rarely included in orthoptic reports. In acquired paresis or paralysis of one of the vertically acting extraocular muscles, especially one of the obliques, some degree of torsional deviation is usually present. However, this form of deviation is usually slight and is often missed if testing is not carried out adequately in all positions of binocular gaze.

With the increasing incidence of automobile accidents involving the ocular muscles the number of cases of paretic cyclodeviation for which surgical interference is indicated is increasing. In recent times a number of direct and indirect surgical approaches have been described (Duke-Elder and Wybar, 1973) to correct this defect or to reduce it sufficiently so that it can be controlled by normal torsional fusional reserve. Since in the present state of our knowledge it is difficult to state exactly how much of a particular procedure is to be carried out to correct a definite degree of torsion, one has to be prepared to carry out the surgical treatment in stages. Therefore in modern strabismological practice it is essential to measure cyclodeviation in all cardinal positions of gaze repeatedly not only for proper surgical planning but also for correct evaluation of the effectiveness of a particular procedure.

The method described here has been found to be simple, accurate to detect even the smallest degree of cyclodeviation, and most convenient to perform in all the 9 cardinal positions of binocular gaze. These slides can also be used to measure horizontal and vertical deviations accurately. The disadvantage of the method is that it cannot be used in young children, in whom the objective method of noting torsional deviation during examination of ocular motility may be the only method practicable.

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Unusual ocular presentation of acute toxoplasmosis

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SUMMARY Four patients with toxoplasmosis are reported with unusual presenting ocular lesions. One patient had an active lesion that appeared to involve the optic nerve as well as focal toxoplasmosis chorioretinitis at the macula. A second patient had a pale optic nerve in association with the classical chorioretinal scars of toxoplasmosis. The third patient had toxoplasmosis chorioretinitis of the macula with subretinal neovascularisation. The fourth patient had a branch artery occlusion complicating acute retinitis.

Our report includes 4 patients with unusual manifestations of toxoplasmosis. Optic neuritis and/or optic atrophy was present in 2 patients. A subretinal neovascular frond was present in a third patient. The fourth individual had a branch artery occlusion involving a vessel which passed through an area of acute toxoplasmosis chorioretinitis.

Although retinitis occurring at the macula, the retinal periphery, or even in a juxtapapillary position occurs commonly, optic nerve involvement in toxoplasmosis is rare (Hogan *et al.*, 1964). In addition, we are not aware of a previous report in which either subretinal neovascularisation or a branch artery obstruction has been reported in association with acute toxoplasmosis chorioretinitis. Since these complications can add confusion to the diagnosis of acute toxoplasmosis, we believe they warrant documentation.

Case reports

PATIENT 1

A 15-year-old Caucasian male awoke 3 weeks prior to examination with decreased visual acuity in the right eye (OD). He denied other symptoms and had been in good health. Family pets included 5 new kittens and 1 dog. Ophthalmological examination 5 years previously documented visual acuity of 20/20 in both eyes (OU). On examination at the Medical College of Wisconsin (MCOW) his visual acuity was 10/200 OD and 20/20 in the left eye (OS). A positive Marcus-Gunn pupillary response (i.e., afferent conduction defect) was present OD. There were mutton-fat keratic precipitates (kp) OD, but not OS. The anterior chamber had 2+ cells OD and 1+ flare. The vitreous had 1 to 2+ cells anteriorly and 3 to 4+ posteriorly. An elevated, one disc diameter, intraretinal exudative lesion of the macula was present with overlying vitreous cells (Fig. 1). The disc was oedematous; at the temporal margin there

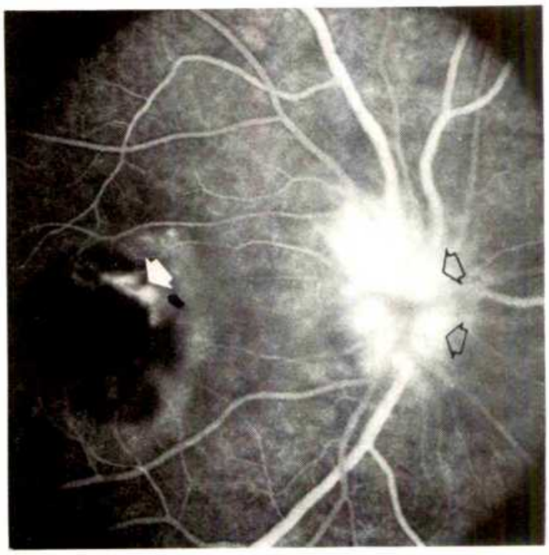

Fig. 1 *Patient 1: Venous phase of fluorescein angiogram OD which demonstrates dye leaking from the active lesion at the optic disc* (open arrows). *There is obstruction of fluorescence by the acute retinitis at the macula except at the margins of the lesions. There is a suggestion of a subretinal neovascular frond present at 1 o'clock in the perifoveal area* (white arrow), *but it is beyond the resolution of the photographs*

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was intraretinal exudation and sheathing of the retinal vessels, and there were many cells in the vitreous overlying the optic disc. The periphery of the right eye was normal. There were no abnormalities of the left eye. Fluorescein angiogram showed dye actively leaking from three separate foci on the disc and extending beyond the margins (Fig. 1). In the late views the optic nerve head was completely obscured by fluorescein leakage (Fig. 2). The macular lesion blocked fluorescence centrally but leaked progressively at the margins. There was a suggestion of subretinal neovascularisation (Figs. 1 and 2, perifoveal area at 1 o'clock), but a definite frond could not be identified. The Sabin-Feldman dye titre was 1:32 and the indirect immunofluorescence antibody titre for toxoplasmosis was 1:256. Complement fixation titre was 1:8. Skin test for histoplasmosis was negative. At follow-up examinations over a 6-month period his visual acuity remained 20/200 OD, and the Marcus-Gunn pupillary response persisted.

Comment: This patient illustrates acute optic neuritis associated with an active toxoplasmic lesion involving the macula. The optic nerve oedema and fluorescein angiography characteristics appear to be due to intrinsic inflammation within the nerve head, not to the macular lesion, evidenced by the persistent afferent pupillary response defect after quiescence of the inflammation.

PATIENT 2

An 18-year-old female had optic neuritis diagnosed in her left eye at age 16, accompanied by visual loss and bitemporal and occipital headaches. Approximately 1 year later blurring of vision recurred OS, with a mild, right temporal headache. Her ophthalmologist noted retinal scars suggestive of ocular toxoplasmosis, and she was given treatment for toxoplasmosis. Vision fluctuated over the next 3 months, at which time she was seen in consultation at MCOW and noted to have visual acuity of 20/20 OD and 20/20–2 OS. A definite positive Marcus-Gunn pupillary response was present OS. An atrophic chorioretinal scar with pigment at its margins was present superonasal to the disc OS (Fig. 3). Vitreous condensation extended from the side of the lesion to the disc and into the vitreous body. Inferonasal to the disc was another punched-out area of chorioretinal atrophy, with a large choroidal vessel visible (Fig. 3). Neither of these lesions appeared active. The disc was pale. The macula was normal, and there was no vascular attenuation. The fundus of the right eye appeared normal. Fluorescein angiography showed some dilated capillaries on the disc OS with a peripapillary rim of atrophy, but no dye leaking from the disc (Fig. 4). The peripheral scars blocked fluorescence except at their margins, where staining occurred. At 30 minutes there was diffuse staining of the disc as well as the adjacent sclera. The patient was next

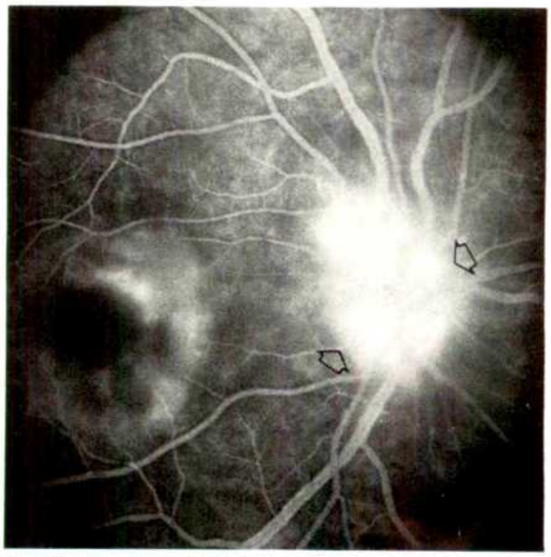

Fig. 2 *Patient 1: Late frame of fluorescein angiogram OD. Note the increase in fluorescein leakage from the disc* (open arrows)

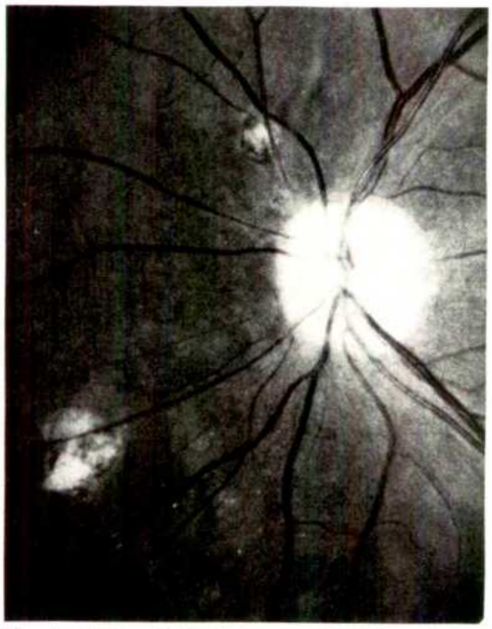

Fig. 3 *Patient 2: Kodachrome taken with red-free light OS demonstrates typical toxoplasmosis chorioretinal scars and pale optic disc*

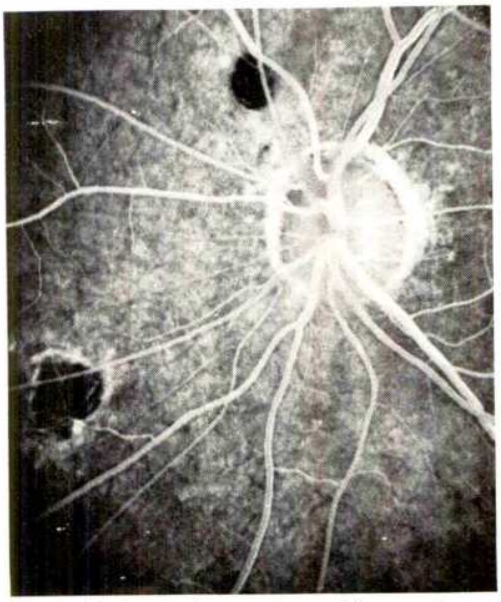

Fig. 4 *Patient 2: Venous phase of fluorescein angiogram OS demonstrates dilated capillaries on the disc with peripapillary hyperfluorescence, but no dye leaking from the disc surface*

seen 1½ years later with an active, recurrent satellite lesion. Visual acuity was 20/25 OS. One month later her visual acuity had returned to 20/20 +2 OS, but the afferent nerve conduction defect remained present.

Comment: This patient has typical chorioretinal lesions of toxoplasmosis and a history of optic neuritis evidenced by a Marcus-Gunn pupillary response and pallor of the optic disc.

PATIENT 3

A healthy 15-year-old male on no medications complained of blurred vision OS for 4 weeks. He had no previous history of ocular disease, and visual acuity had been normal 5 months earlier. Examination showed a visual acuity of 20/20 OD and 10/200 OS. A positive Marcus-Gunn pupillary response OS was present. The anterior chamber was clear OU. The anterior vitreous was clear OD, but had 2+ cells OS. Indirect ophthalmoscopy showed a normal fundus OD. The disc margin OS was oedematous and slightly elevated, with a dusky pigmentation from the 6–12 o'clock position. The macula had a subretinal white, round, elevated lesion (Fig. 5), with retinal striae extending nasally and temporally from the lesion. Vitreous precipitates were present on the back of the retracted vitreous face. Amsler-Grid revealed an absolute central scotoma which extended 10° vertically and 12° horizontally. Fluorescein angiography demonstrated subretinal neovascularisation at the macula (Fig. 6), with dye leaking progressively from the neovascular frond into the subretinal space (Fig. 7). Indirect immunofluorescence titre for toxoplasmosis was 1:16. The patient underwent treatment with prednisone, pyrimethamine, and sulphadiazine. One year later the macular lesion was inactive and the disc appeared normal. An afferent conduction defect pupillary response was no longer present.

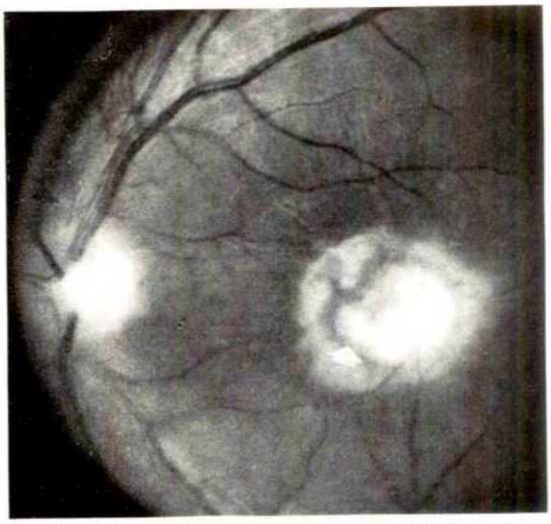

Fig. 5 *Patient 3: Kodachrome using red-free light OS demonstrates the retinitis at the macula with retinal striae extending from it* (white arrow)

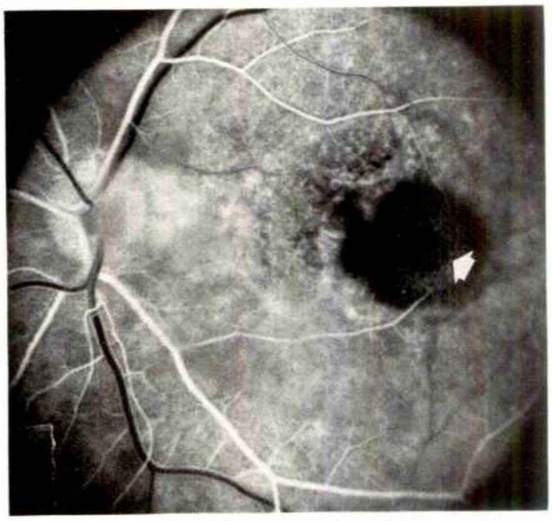

Fig. 6 *Patient 3: Early venous phase of fluorescein angiogram OS demonstrating the subretinal neovascular frond* (white arrow)

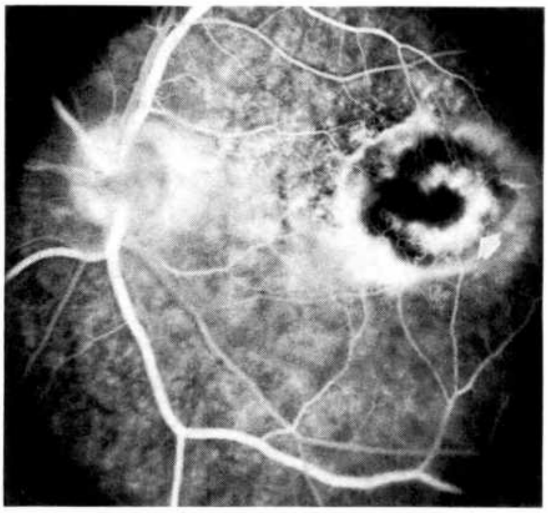

Fig. 7 *Patient 3: Late venous phase of fluorescein angiogram OS demonstrating dye leaking from subretinal neovascular frond* (white arrow)

Comment: The patient had subretinal neovascularisation as shown by fluorescein angiography, associated with toxoplasmosis chorioretinitis. Although the disc was originally oedematous with an afferent conduction defect of the nerve, the inflammation apparently was secondary to the macular lesion, since later examination revealed neither optic atrophy nor persistent conduction defect.

PATIENT 4

A 17-year-old male had no visual difficulties until 10 days prior to consultation at the MCOW, when metamorphopsia OS was noted. On examination visual acuity was 20/15 OD and 20/200 OS. Small, white keratic precipitates were present OS with 1+ cellular reaction and flare in the anterior chamber. The cornea and anterior chamber OD were clear and the fundus examination was normal. Fundus examination OS revealed an intense retinitis in the superior portion of the macula (Fig. 8) with subretinal fluid along the inferior margin. There was localised intraretinal haemorrhage and a branch artery obstruction of an arteriole passing through the area of retinitis. Fluorescein angiogram showed the area of non-perfusion resulting from the branch artery obstruction as well as fluorescein leakage in the area of retinitis (Fig. 9). The Sabin-Feldman dye titre was 1:256. He was treated with sulphadiazine, pyrimethamine, folinic acid, and prednisone, with resolution of the acute chorioretinitis.

Comment: This case showed a branch artery occlusion originating at the locus of acute toxoplasmosis chorioretinitis. Branch vascular occlusion, which can obscure the inflammatory focus, should alert the ophthalmologist to the possibility of underlying toxoplasmosis chorioretinitis when present in a young patient with cellular infiltrate in the vitreous.

Discussion

Ocular toxoplasmosis is caused by a non-motile obligate intracellular parasite, *Toxoplasma gondii*. It may occur in either a congenital or acquired form. Clinically the ocular lesion in either form usually

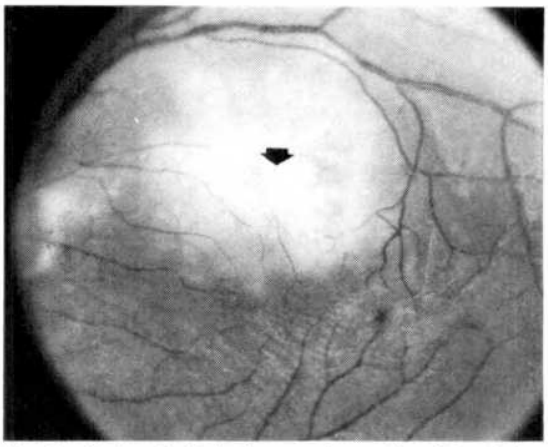

Fig. 8 *Patient 4: Kodachrome taken with red-free light OS which demonstrates the area of acute retinitis with the attenuated arteriole passing through it* (dark arrow)

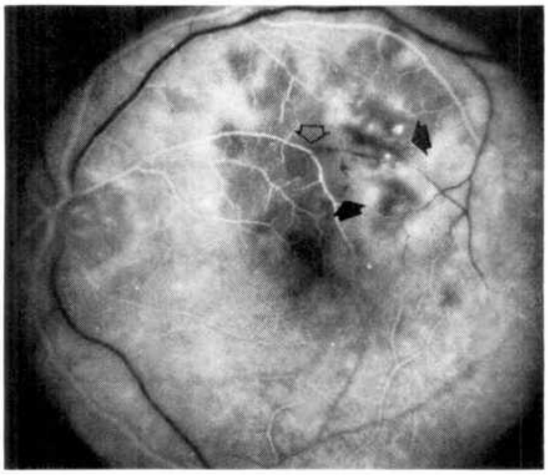

Fig. 9 *Patient 4: Arterial phase of fluorescein angiogram OS which demonstrates that the attenuated arteriole passing through the acute retinitis does not fill with dye, with complete obstruction of the arteriolar branch at the bifurcation* (open arrow) *and surrounding areas of capillary non-perfusion* (dark arrows)

presents as a focal necrotising chorioretinitis. Recurrences are common as satellite lesions adjacent to an old atrophic scar or in an area of previously normal-appearing retina. The inflammation may be self-limited or in some instances fulminating, resulting in endophthalmitis (Duke-Elder, 1966; Gass, 1970). Juxtapapillary lesions are less common. An active lesion in the optic nerve is rare (Walsh and Hoyt, 1969).

While cranial nerve involvement has been described (Koch, 1943) and papilloedema may be secondary to lesions in the CNS (Koch, 1943), the optic nerve of Patient 1 appears to have been directly affected as well as there being a classical lesion involving the macula (Figs. 1, 2). There were no CNS symptoms or signs to suggest secondary papilloedema. In addition the disturbance of the optic disc was unilateral, the visual acuity was acutely and severely decreased, and a Marcus-Gunn pupillary response was present and persisted.

Patient 2 had a pale optic disc in association with typical chorioretinal scars (Figs. 3, 4). An attack of recurrent acute inflammation occurred as a satellite lesion, which is characteristic of toxoplasmosis. It is possible that the patient had both toxoplasmosis chorioretinitis and a separate cause of the pale disc. Zimmerman, however, noted *Toxoplasma gondii* in the optic nerve in a case of ocular toxoplasmosis (Zimmerman, 1961). Others have suggested that some cases of optic neuritis in young adults may be caused by toxoplasmosis (Hogan *et al.*, 1964; Frenkel and Jacobs, 1958; Frezzotti and Guerra, 1963).

Patient 3 presented acutely with subretinal neovascularisation (Figs. 5, 6, 7). Patient 1 also had the appearance of subretinal neovascularisation in the chorioretinitis which occurred at the macula (Figs. 1, 2), but photographic resolution did not permit absolute identification of the frond. Retinociliary anastomotic vessels have been previously reported in chorioretinal scars due to toxoplasmosis (Gass, 1970; Saari *et al.*, 1975; Kennedy and Wise, 1971). In addition, a racemose angioma of the retina has been described in association with toxoplasmosis (Stucchi *et al.*, 1972) as well as preretinal fibrovascular proliferans extending from the disc to a chorioretinal lesion (Saari *et al.*, 1975; Maumenee, 1961). We are unaware of a previous case in which a neovascular frond was present like that in Patient 3. The patient had no history of trauma, was not myopic, and had no peripheral scars such as are seen in presumed ocular histoplasmosis. He did not have angioid streaks. Although the possibility of *Toxocara canis* was considered, the clinical appearance and reactive immunofluorescence antibody titre seemed to confirm the diagnosis of toxoplasmosis.

Retinal vascular lesions previously reported in toxoplasmosis include periphlebitis with or without venous insufficiency, concomitant periphlebitis and periarteritis, and rarely segmental periarteritis alone (Schwartz, 1977; Wise *et al.*, 1971). Patient 4 presented with a branch artery obstruction as the vessel passed through a localised area of acute retinitis (Figs. 8, 9).

Serological tests for toxoplasmosis include the Sabin-Feldman dye test, indirect fluorescent antibody test, complement fixation test, precipitin test, and haemagglutination test. A skin test has also been used but may not become positive until as long as 6 months after infection (Hogan *et al.*, 1964; O'Connor, 1957; Huldt, 1958; Jacobs and Lunde, 1957; Scott, 1974). A Sabin-Feldman dye titre of 1:16 or greater has been considered positive (Hogan *et al.*, 1964; Scott, 1974). Hogan *et al.* reported an unusual patient with a positive dye titre only in undiluted serum but who had toxoplasma organisms in his eye at necropsy (Hogan *et al.*, 1964). Others have found equally low Sabin-Feldman dye titres in histologically proved cases, including 1 case which was seronegative (Zscheile, 1964; Franceschetti and Engelbrecht, 1964). There has been good agreement (95%) between the Sabin-Feldman dye test and the indirect fluorescent antibody test regarding their specificity and sensitivity (Scott, 1974; Walton *et al.*, 1966). Positive titres in either test can exist for years, and it has been suggested that variations in serum titres tend to reflect proliferative activities of the parasite in the reticuloendothelial organs more than the activity of eye lesions (Scott, 1974; O'Connor, 1973). Patient 1 had a dye titre of 1:16 and an indirect fluorescent antibody titre of 1:64. Patient 2 did not have serological testing but had classical peripheral chorioretinal scars associated with toxoplasmosis. Patient 3 had an indirect fluorescent antibody titre of 1:16. Patient 4 had a Sabin-Feldman dye titre of 1:256. None of our patients had evidence of systemic lupus erythematosus, which may cause a false positive immunofluorescent test for toxoplasmosis.

The 2 cases in this report with optic nerve involvement emphasise the need to include toxoplasmosis in the differential diagnosis of any patients presenting with optic neuritis. In addition they suggest the importance of carefully testing patients with peripheral toxoplasmosis chorioretinitis for a Marcus-Gunn pupillary response to rule out concomitant occult optic nerve involvement. The third patient indicates that toxoplasmosis should be included in the differential diagnosis of subretinal neovascularisation, particularly in the young. Finally, the fourth patient demonstrates that branch artery occlusion may complicate toxoplasmosis chorioretinitis.

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HLA-B27 frequency in Greek patients with acute anterior uveitis

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SUMMARY The histocompatibility antigen HLA-B27 was identified in 12 out of 33 patients with acute non-granulomatous anterior uveitis. This is a frequency of 36·36%, compared with 4·72% in controls. Seven patients had in addition evidence of systemic disease, including ankylosing spondylitis, sacroiliitis, Reiter's disease, Still's disease, and rheumatoid arthritis. Five of these were HLA-B27 positive, which suggests that the uveitis in many of these cases has a similar aetiology to the uveitis in those with rheumatic disease. It appears that the more severe cases of acute anterior uveitis are related more frequently to the presence of HLA-B27.

Associations between HLA-B27 and rheumatic diseases such as ankylosing spondylitis (AS), Reiter's disease (RD), psoriatic arthritis (PA), juvenile rheumatic arthritis (JRA) with sacroiliitis and spondylitis have been described (Brewerton *et al.*, 1973a; Schlosstein *et al.*, 1973; White *et al.*, 1972). Investigations concerning analogous associations between HLA antigens and acute anterior uveitis (AAU) have also been reported (Russell *et al.*, 1972; Brewerton *et al.*, 1973b; Mapstone and Woodrow, 1975; Rebmann *et al.*, 1976). Acute anterior uveitis as a disease of the anterior part of the eye usually accompanies certain rheumatic diseases. The aetiology and pathogenesis of this disease are unknown. Though the exact relationship between AAU and rheumatic diseases is obscure, it is obvious from the study of the histocompatibility antigens that the incidence of HLA-B27 in both conditions is increased. The meaning of this observation for the pathogenesis, aetiology, and epidemiology of these conditions remains to be elucidated.

Since the distribution of HLA antigens varies in different ethnic groups (Kissmeyer-Nielson, 1972) we undertook to examine the distribution of HLA antigens in Greek patients with AAU.

Material and methods

PATIENTS

Thirty-three patients with acute anterior uveitis (non-granulomatous) were referred to the ophthalmological clinic of Vasilevs Pavlos Hospital and carefully documented throughout the attack. Diagnosis was based on clinical symptoms and signs. The latter were obtained by a complete ophthalmological examination, that is, inspection with lateral illumination, slit-lamp examination, ophthalmoscopy, and tonometry. Apart from the symptoms suffered by the patients (photophobia, pain, excessive lachrymation), emphasis was given to the following signs: circumcorneal flush, presence of inflammatory cells in the anterior chamber, inflammatory processes of the iris, precipitates on the posterior surface of the cornea, and increased intraocular pressure.

All patients were submitted to a detailed clinical and laboratory examination. Particular attention was paid to the detection of any rheumatic disease. Routine *x*-rays of chest and sacroiliac joints were carried out, with further *x*-rays being taken when indicated.

Among the 33 patients there were 7 who had in addition evidence of systemic disease—ankylosing spondylitis 3, rheumatoid arthritis 1, juvenile rheumatoid arthritis 1, Reiter's disease 1, and sacroiliitis 1.

HLA TYPING

For the identification of the histocompatibility antigens (HLA) on the surface of the lymphocytes the one-stage lymphocytotoxicity micromethod was used (Terasaki and McClelland, 1964) as modified by Kissmeyer-Nielsen and Thorsby (1976-7). The

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panel consisted of 63 specific antisera, so that each antigen was checked at least twice.

In particular, for HLA-B27 3 monospecific and dispecific (B27 and B7) antisera were used. HLA antisera were kindly provided by the National Institutes for Health, Bethesda, Maryland, and Professor Van Rood (Eurotransplant, Leiden).

Results

The distribution of HLA antigens in 33 Greek patients with acute anterior uveitis and in 233 Greeks who had no blood relationship with them (unbiased sample) is shown in Table 1. HLA-B27 was detected in 12 out of 33 patients with AAU, that is, 36·36% instead of 4·72% in the control sample. The frequency difference of HLA-B27 among patients and healthy persons is statistically significant ($\chi^2 = 63{\cdot}05$, $P < 0{\cdot}001$). The relative risk—mostly an indicator of the strength of the association between HLA-B27 and the disease—is 12·66. Of the 12 patients carrying B27, 4 were males (mean age = 36·02) and 8 females (mean age = 29·50) (Table 2). The sex ratio (males/females) is 1:2, while the mean age is greater among the male patients. Table 2 also shows that the concurrence of AAU and systemic disease is greater in males than in females.

HLA-B27 is more frequent in patients with AAU who in addition have a systemic disease (5 out of 7 with systemic disease were B27-positive) than in those with AAU alone.

Table 1 *Distribution of HLA antigens (%) in patients with AAU and controls*

HLA series	*Antigen*	*Patients* *No.*	*Patients* *Frequency (%)*	*No.*	*Sample* *Frequency (%)*
HLA-A	A1	5	15·15	56	24·03
	A2	12	36·30	123	52·79
	A3	12	36·30	50	21·46
	A9	12	36·30	79	33·91
	A10	2	6·10	36	15·45
	A11	4	12·20	19	8·25
	A28	2	6·10	17	7·73
	AW19	3	9·13	26	11·27
	A29	2	6·10	9	3·97
HLA-B	B5	12	36·30	74	31·76
	B7	7	21·20	31	13·30
	B8	2	6·10	27	11·59
	B12	2	6·10	41	17·60
	B13	1	3·03	11	4·72
	B14	3	9·10	16	6·87
	BW15	1	3·03	17	7.30
	BW16	1	3·03	9	3·86
	BW17	2	6·10	16	6·87
	B18	7	21·20	69	29·62
	AW22	—	—	3	1·29
	B27	12	36·36*	11	4·72*
	BW35	8	24·24	40	17·16
	BW40	5	15·15	26	11·16

*$\chi^2 = 63{\cdot}05$, $P < 0{\cdot}001$, relative risk = 12·66

Table 2 *Age and sex of 33 patients with non-granulomatous iridocyclitis*

HLA—B27	+		−	
No.	12		21	
Sex	M 4	F 8	M 7	F 14
Mean age (years)	36·10	29·50	36·74	47·80
Systemic disease	3	2	2	0

Table 3 *Relationship of HLA-B27 antigen with various clinical manifestations (33 patients)*

	HLA—B27			
Clinical manifestation	*Positive* *No.*	(12) (%)	*Negative* *No.*	(21) (%)
Exudates	12	(100)	18	(85·71)
Hyaloid precipications	7	(58·33)	4	(19·04)
Recurrent attacks	11	(91·66)	9	(42·85)
Duration more than 3 weeks	9	(75)	8	(38·09)

Table 3 shows the relationship between B27 and certain clinical findings. Exudates in the anterior chamber are associated with a high frequency of B27 antigen. Furthermore, hyaloid precipitates, recurrent attacks, and disease duration longer than 3 weeks are associated with a higher frequency of B27.

Discussion

The findings in this small series of Greek patients did not differ significantly from those in previous studies of acute anterior uveitis. The main finding was that HLA-B27 in AAU is 36·36% compared with 4·72% of controls. Rebmann *et al.* (1976) reported a frequency of 33·2%, though Brewerton *et al.* (1973b) and Mapstone and Woodrow (1975) reported a frequency of 55%. In comparing the reported frequencies the percentage of patients with systemic disease in the samples should be borne in mind. Thus, in the series of Brewerton *et al.* (1973b) 45·5% had systemic disease and in the series of Mapstone and Woodrow (1975) 31%. In our series only 21% had systemic disease. The presence of B27 in patients of this group with AAU who in addition had systemic disease was 71·4%, which is not significantly different from those reported by

Brewerton *et al.* (1973b) (85%) and Mapstone and Woodrow (1975) (82%). The association between non-granulomatous AAU and rheumatic disease deserves emphasis, and at least in this study B27 may represent an important link.

The B27 frequency in patients with AAU who did not have any systemic disease was 27%, about the same as that reported (Brewerton *et al.*, 1973b (29%)). Cases of AAU which had exudates in the anterior chamber were accompanied by a high frequency of B27. This is in accord with ankylosing spondylitis, which is commonly accompanied by exudates. It is well known that the incidence of B27 in ankylosing spondylitis is very high (Brewerton *et al.*, 1973a; Schlosstein *et al.*, 1973; White *et al.*, 1972).

The observation that there is a striking association between B27, acute anterior uveitis, ankylosing spondylitis, Reiter's disease, and psoriatic arthritis provides evidence for a common pathogenesis. The presence of B27 alone does not necessarily lead to a particular clinical disease, but possibly it provides a background for uncommon disease association. Dick and her colleagues (1974) described a family in which out of 2 sibs carrying B27 only 1 had ankylosing spondylitis. There was seemingly a cross-over effect dissociating the gene for B27 antigen from that responsible for increased liability to AS. It was concluded that it is not the possession of antigen B27 alone which determines the manifestation of a certain disease but that the existence of an adjacent gene for disease susceptibility—perhaps an Ir gene—is necessary.

Different strengths of association between B27 and uveitis—or other disease—in different ethnic groups may provide information on the antigen responsible and the co-working factor.

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Bull's eye maculopathy with early cone degeneration

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SUMMARY Seven patients with acquired cone degeneration were investigated. The initial visual acuities in 6 of the series were normal or near normal but later deteriorated, although they did not fall below 6/60 in any patient. All the patients tested had colour vision defects and abnormalities on electrodiagnostic testing referable to the cone system. The typical picture was of a bull's eye maculopathy accompanied by an annular scotoma around the fovea, but the clinical and electrophysiological investigations showed that there were considerable variations especially in the early stages.

Bull's eye maculopathy has a characteristic appearance; there is a dark central area at the fovea with a paler zone around it. Round the pale area there is frequently a hyperpigmented ring. The changes are nearly always bilateral and appear symmetrical. This abnormality of the macula can be caused by several disorders of the retina and pigment epithelium. Drug toxicity, the cone dystrophies, central serous retinopathy, senile predisciform macular degeneration, dominant macular dystrophy, fundus flavimaculatus, and Batten Mayou disease have all been described with this appearance (Weise and Yannuzzi, 1974; Deutman, 1974; Kearns and Hollenhorst, 1966).

The acquired cone dystrophies are recognised by the triad of signs: diminished visual acuity, diminished colour vision, and abnormalities of the photopic portion of the electroretinogram (Goodman *et al.*, 1963; Krill, 1966; Krill and Fishman, 1971; Kelsey and Arden, 1972). In cases of acquired cone dystrophy a bull's eye degeneration of the macula is a well-recognised feature (Sloan and Brown, 1962; François, 1974) although the fundus may appear either normal or with pigment granularity of the macula or with choroidal atrophy (Steinmetz *et al.*, 1956; Babel and Stangos, 1972; Krill *et al.*, 1973; Ohba, 1974).

The present series of patients, with one exception, attended early in the course of their disease and, when they were symptomatically only mildly affected, showed various features which may be misleading in making the diagnosis. They were investigated and assessed to see whether a common pattern and disease entity could be found.

Patients and methods

The 7 patients in this series presented to Moorfields Eye Hospital for further investigation of failing vision. They were referred to the retinal diagnostic department between 1969 and 1975 either by outside ophthalmologists or by other consultants on the staff at Moorfields.

With the exception of Case 4, who had an affected relative, the patients all had a bull's eye appearance of their maculae similar to that already described.

They were investigated further with refraction, visual field testing, colour vision assessment, electrodiagnostic studies, and colour and fluorescein photography.

Field charting was performed on a Bjerrum screen with either 1/1000 or 2/1000 test objects. Initially, Goldmann perimeter fields were also attempted, but it was found that with some patients with a small central island of sparing the test object disappeared in the central fixation spot. With the Bjerrum screen the patients had no difficulty with fixation owing to their 'tunnel' vision, and were easily able to see the test object close to the central fixation spot.

Colour vision was assessed with Hardy Rand Rittler isochromatic plates under standard illumination. Farnsworth Munsell 100 hue testing was also attempted on 5 patients, but on only 1 was a reliable test obtained. Two patients had visual acuities which precluded 100 hue testing, and the other 2 patients had such poor colour vision they were incapable of performing the test.

Colour photography was performed with a Carl Zeiss Jena (Retinophot) camera using Kodak Ektachrome X film (ASA 64). Fluorescein angiography was carried out by injection of 5 ml of 20%

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sodium fluorescein into an antecubital vein. The photographs were taken on a West German Zeiss fundus camera using Ilford FP4 film (ASA 125). The excitatory filter was a Baird atomic B5 and the barrier filter an Ilford 109.

Electrodiagnostic tests were performed on all patients. These included an electro-oculogram (EOG), photopic and scotopic electroretinogram (ERG), and critical fusion frequencies (CFF). A flash visually evoked response (VER) was performed on 2 patients and a pattern VER on 5 patients.

The EOG was carried out as described by Arden *et al.* (1962). 30 degree eye movements were made between fixation lights, and the electrical potentials were recorded on a Medelec MS6 machine.

The ERG technique was based on that used by Karpe (1945). A haptic contact lens was used with the electrode and the pupil was dilated. The light source was a xenon stroboscope.

The visually evoked responses were recorded either on a Medelec MS6 or computer of average transients. The stimuli in some cases were flashes of light and in others were reversing checkerboard patterns. The checkerboard patterns varied in size from 11·5′ arc to 46′ arc and in contrast from 20 to 50%. The reversals were mostly at 10 Hz but some patients were tested with 2 Hz.

Follow-up on the patients varied from 6 months to 7 years. One patient was seen on only 1 occasion as she then returned home overseas.

Case Histories

CASE 1

A 35-year-old white man presented to the hospital in 1969 with defective vision and mild photophobia. Six years previously he had 6/6 vision in each eye with a myopic correction. *Visual acuity:* 6/24 right, 6/9 left. *Fundi:* typical bull's eye appearance of the maculae (Fig. 1). *Fields:* central scotoma in each eye; no central island of sparing was demonstrated. *Fluorescein angiography:* bilateral hyperfluorescent oval ring from the intact choriocapillaris underlying the pale area of pigment epithelium (Fig. 1). *Heredity:* his parents had good vision with suitable glasses; he had no siblings. His 4 children had normal visual acuities, colour vision to HRR plates, and opthalmoscopically normal fundi.

Follow-up: 5 years later he was reassessed and further investigated. *Visual acuities:* 6/60 right and left. *Fundi:* increase in size of the bull's eye (Fig. 1). *Colour vision:* HRR—marked protan, deutan, and tritan defect. 100 hue—not possible. *Fluorescein angiography:* increase in the area and density of the transmission defect (Fig. 1). *Electrodiagnostic tests:* EOG: 213% right, 240% left. ERG: reduced photopic b-wave right and left. CFF: >60 right and left. VER: (2 Hz, 20% contrast, 46′ arc squares) markedly reduced amplitudes with normal conduction times.

CASE 2

A 28-year-old white man had been noted in 1969 to have very poor colour vision, but no other ocular abnormality was detected. He presented in 1971 complaining of loss of vision, especially when watching a moving ball. His general health was good although he had suffered a bout of malaria in 1970. For this he was treated with chloroquine sulphate 200 mg weekly for 6 months (i.e., a total dose of chloroquine of approximately 5 g), and he was then treated with pyrimethamine 25 mg weekly, which was continued prophylactically. *Visual acuities:* 6/9 in each eye with myopic correction. *Fundi:* normal. *Fields:* ring scotoma around central fixation from 2° to 4° (Fig. 2). *Colour vision:* HRR plates showed severe red-green and moderate blue-yellow defects. *Fluorescein angiography:* normal. *Electrodiagnostic tests:* EOG: within normal limits—right 223% and left 181%. ERG: scotopic ERG: normal photopic ERG: reduced b-wave. CFF: 40 right and left. VER: (10 Hz 23′ arc squares, 20% contrast) grossly reduced amplitudes. *Heredity:* there was no family history of poor central vision.

Follow-up: three years later he was reviewed. *Visual acuities:* 6/18 right and 6/24 left. *Fundi:* right normal; left bull's eye maculopathy. *Fields:* unchanged. *Fluorescein angiography:* bilateral pigment epithelial transmission defects (Fig. 3).

CASE 3

A 37-year-old white man was diagnosed in October 1971 in another ophthalmic unit as having macular degeneration. His vision was 6/9 right, 6/6 left with paracentral scotomata. He was first seen in Moorfields Eye Hospital in March 1973. *Visual acuities:* 6/12 right, 6/6 left, with myopic correction. *Fundi:* typical bull's eye appearance in both eyes (Fig. 4). *Fields:* (Goldmann perimetry) bilateral scotomata of the central 5°. *Colour vision:* HRR plates: mild red-green defect. Farnsworth Munsell 100 hue test: tritan defect in the right eye with a suggestion of a similar defect in the left eye (Fig. 5). *Fluorescein angiography:* annulus of transmission defect around the fovea (Fig. 4). *Electrodiagnostic tests:* EOG: 170% right and left. *Heredity:* this patient had a dominant family history of macular disease. His mother and aunt had been known to have macular degeneration since an early age; unfortunately, they could not be investigated. His brother also had macular degeneration from an early age and is

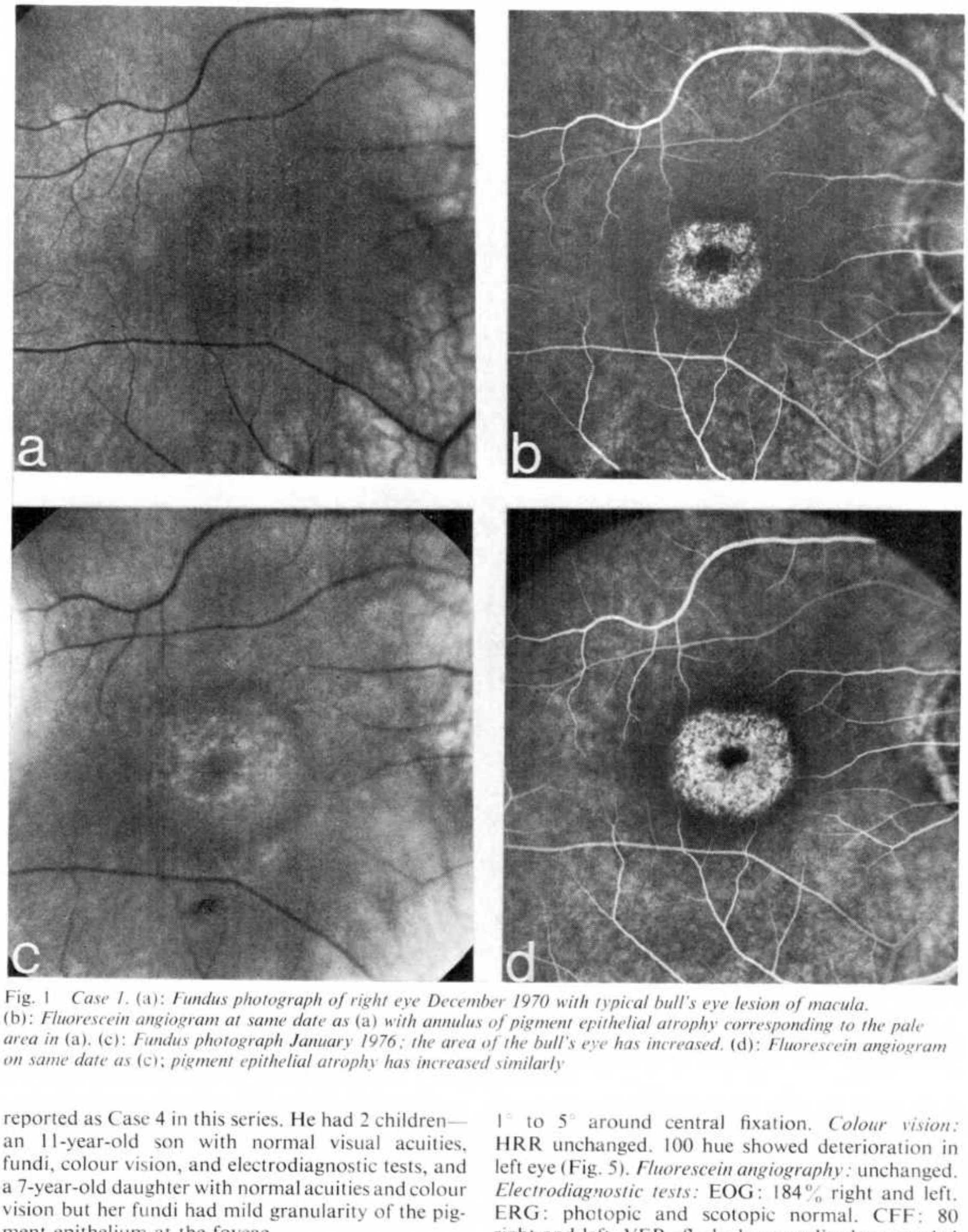

Fig. 1 *Case 1.* (a): *Fundus photograph of right eye December 1970 with typical bull's eye lesion of macula.* (b): *Fluorescein angiogram at same date as* (a) *with annulus of pigment epithelial atrophy corresponding to the pale area in* (a). (c): *Fundus photograph January 1976; the area of the bull's eye has increased.* (d): *Fluorescein angiogram on same date as* (c); *pigment epithelial atrophy has increased similarly*

reported as Case 4 in this series. He had 2 children—an 11-year-old son with normal visual acuities, fundi, colour vision, and electrodiagnostic tests, and a 7-year-old daughter with normal acuities and colour vision but her fundi had mild granularity of the pigment epithelium at the foveae.

Follow-up: 2 years later. *Visual acuities:* 6/12, 6/9. *Fundi:* no change. *Fields:* annular defect from 1° to 5° around central fixation. *Colour vision:* HRR unchanged. 100 hue showed deterioration in left eye (Fig. 5). *Fluorescein angiography:* unchanged. *Electrodiagnostic tests:* EOG: 184% right and left. ERG: photopic and scotopic normal. CFF: 80 right and left. VER: flash: low amplitudes recorded with delay of 220–250 ms pattern: (10 Hz, 50% contrast, 46′ arc squares) minimal responses.

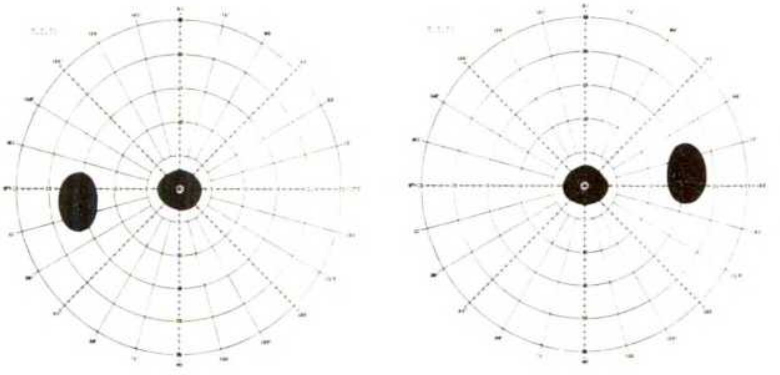

Fig. 2 *Case 2: typical ring scotomata with 1/1000 white objects corresponding to the area of pigment epithelial atrophy in Fig. 3*

CASE 4

A 46-year-old white man, and brother of Case 3, had gradual deterioration of vision over 3 years from the age of 12. *Visual acuities:* 6/60 in each eye with glasses. *Fundi:* well-defined circular area of atrophy of the pigment epithelium underlying both maculae with surrounding multiple, small, white patches in the pigment epithelium (Fig. 6). The central defect was similar to central areolar choroidal sclerosis, although the underlying larger vessels appeared normal. *Fields:* central scotoma in each eye with no central sparing. *Fluorescein angiography:* confirmed the absence of pigment epithelium centrally with atrophy of the choriocapillaries. There were multiple transmission defects corresponding to the small white patches (Fig. 6), but the larger flecks had hypofluorescent centres throughout the angiogram. *Electrodiagnostic tests:* EOG: was reduced 160% right and 155% left. VER: mild reduction in amplitude with normal conduction times to flash stimulus. *Heredity* see Case 3. He had no children.

Follow-up: no follow-up examination was performed on this patient as his disease had been static for 30 years.

CASE 5

A 24-year-old white woman attended her local ophthalmologist in January 1973 complaining of blurred vision in both eyes. Her visual acuities were 6/12 right, 6/6 left with a small myopic correction, and her maculae were seen to have a granular

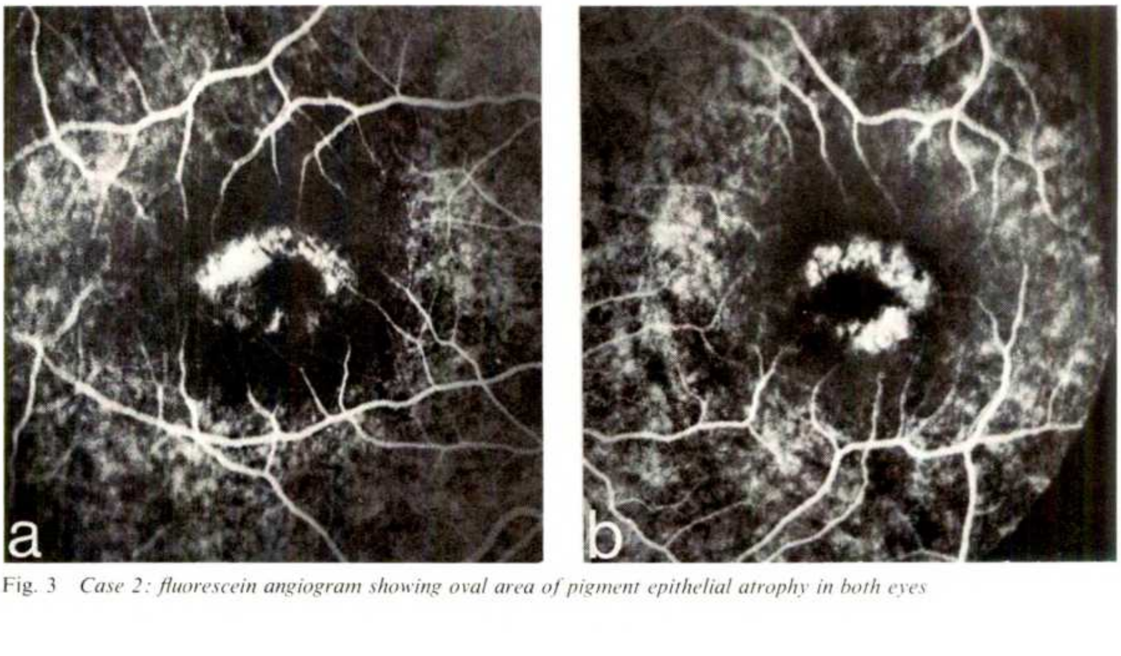

Fig. 3 *Case 2: fluorescein angiogram showing oval area of pigment epithelial atrophy in both eyes*

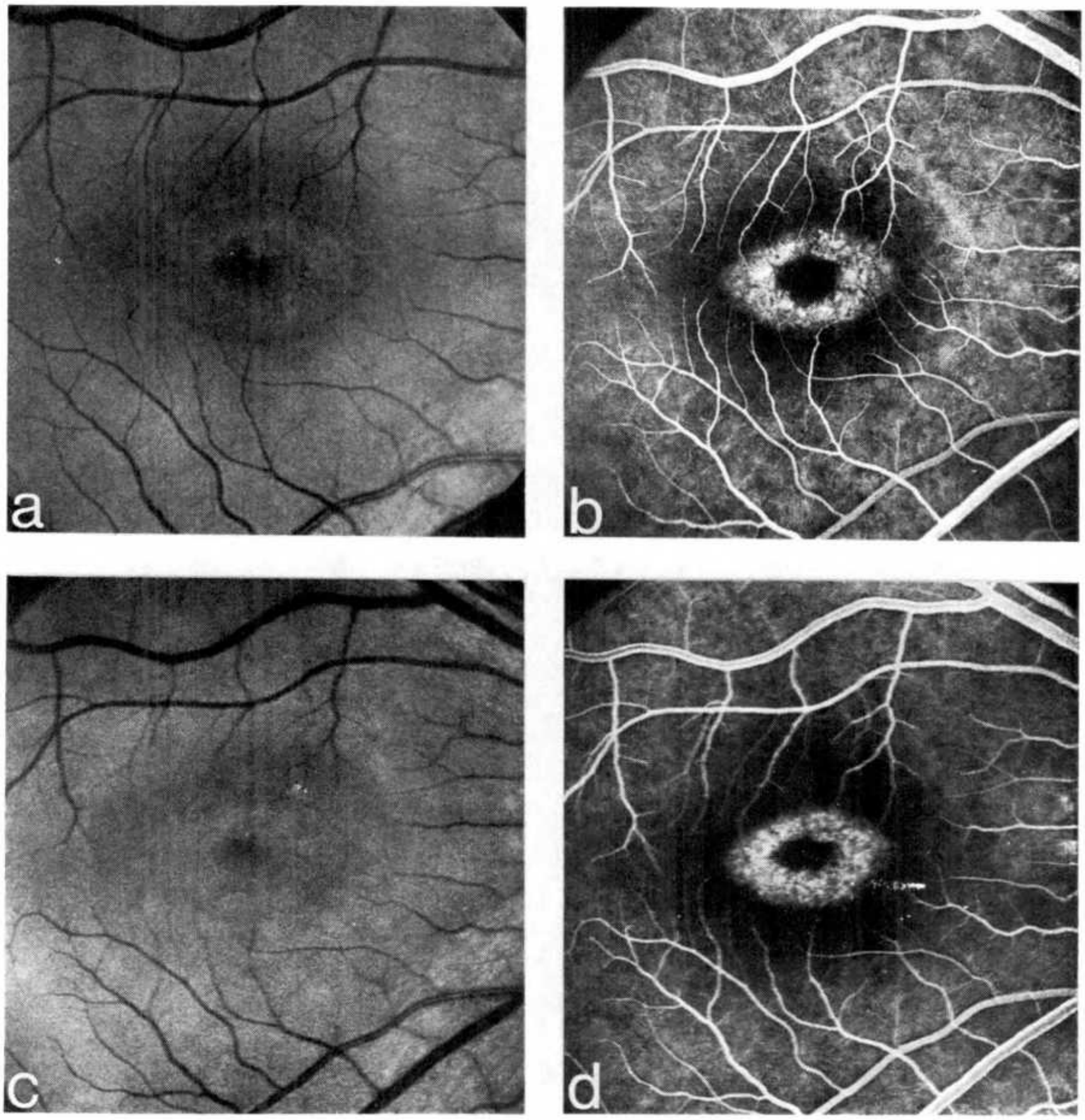

Fig. 4 *Case 3* (a): *Fundus photograph right eye May 1973: typical bull's eye maculopathy.* (b): *Fluorescein angiogram same date as* (a); *annular transmission defect of pigment epithelium.* (c) *and* (d): *Fundus photograph and fluorescein angiogram May 1975 showing no increase in size of affected area*

appearance. A year later her visual acuities were 6/12 right and 6/9 left, and Bjerrum field charting showed a paracentral scotoma in the right eye and an annular defect in the left eye (Fig. 8). She was referred to Moorfields for further investigation. *Visual acuities:* 6/12 right, 6/9 left. *Fundi:* dark central area at the fovea with a perifoveal granular ring of pigment epithelial change. Around this ring was a band of normal looking retina, then a further ring of white flecks in the pigment epithelium (Fig. 7). *Fields:* annular defects right and left (Fig. 8). *Fluorescein angiography:* a hypofluorescent zone centrally with surrounding patches of transmission defect (Fig. 7). The white pigment epithelial lesions were hyperfluorescent and faded as the eye transit progressed. A few larger flecks had hypo-

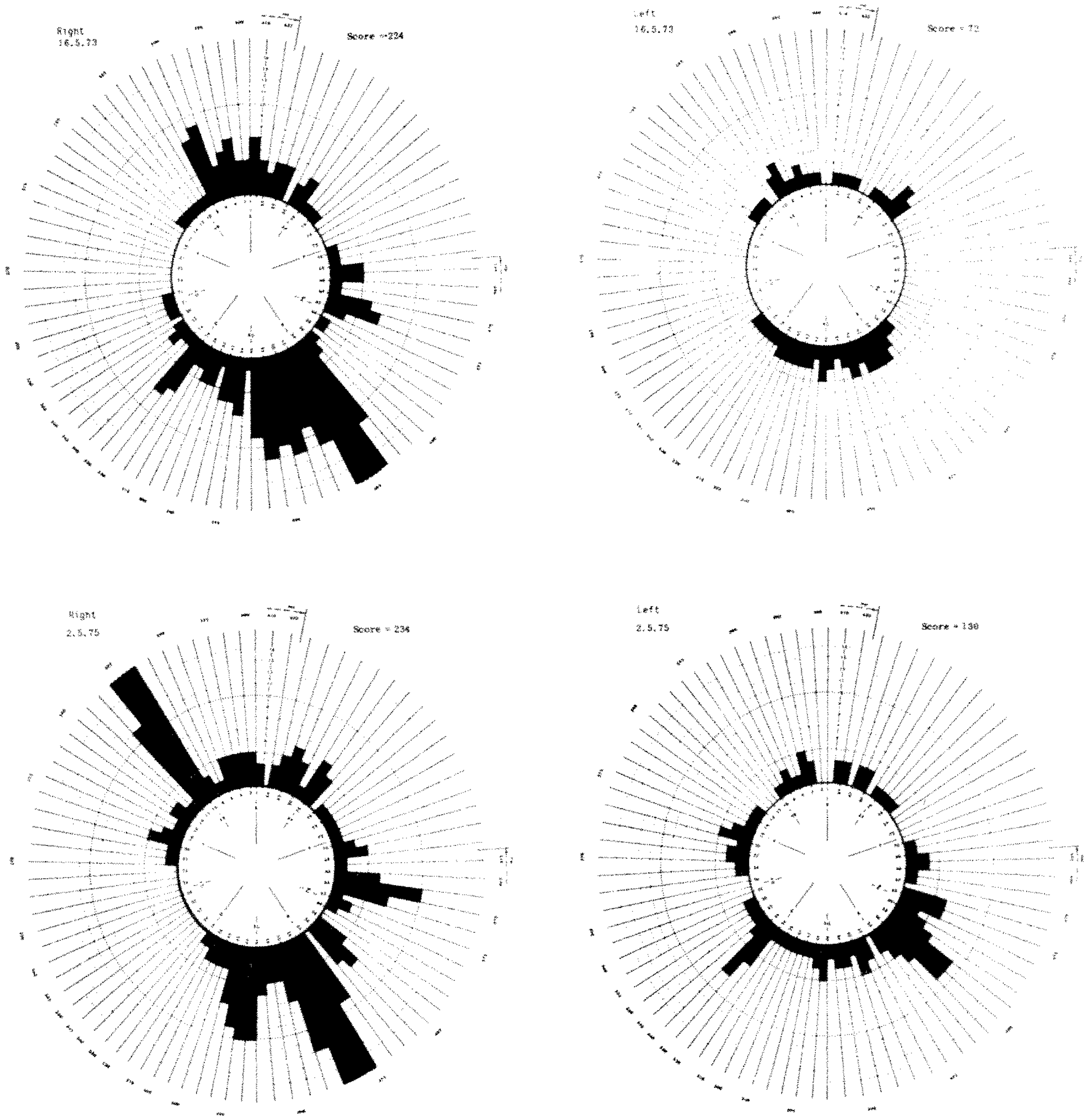

Fig. 5 *Case 3. 100 hue charts of both eyes.* (a) *and* (b): *May 1973.* (c) *and* (d): *May 1975. There is a mild increase in the tritan defect of both eyes*

fluorescent centres throughout the angiogram. *Heredity:* there was no family history of visual disturbance. Her parents had normal vision; she had no siblings.

Follow-up: one year later she was reviewed. *Visual acuities:* 6/12 right; 6/24 left. *Fundi:* unchanged. *Fields:* further extension of ring scotomata (Fig. 8). *Colour vision:* HRR: almost achromatopsic. 100 hue: incapable of performing the test. *Electrodiagnostic tests:* EOG: 155% right and left. ERG: photopic reduced b-wave, scotopic normal. CFF: 16 right and left. VER: (10 Hz 20% contrast 23′ arc squares) extremely low amplitudes.

CASE 6

A 28-year-old white man was seen in February 1974

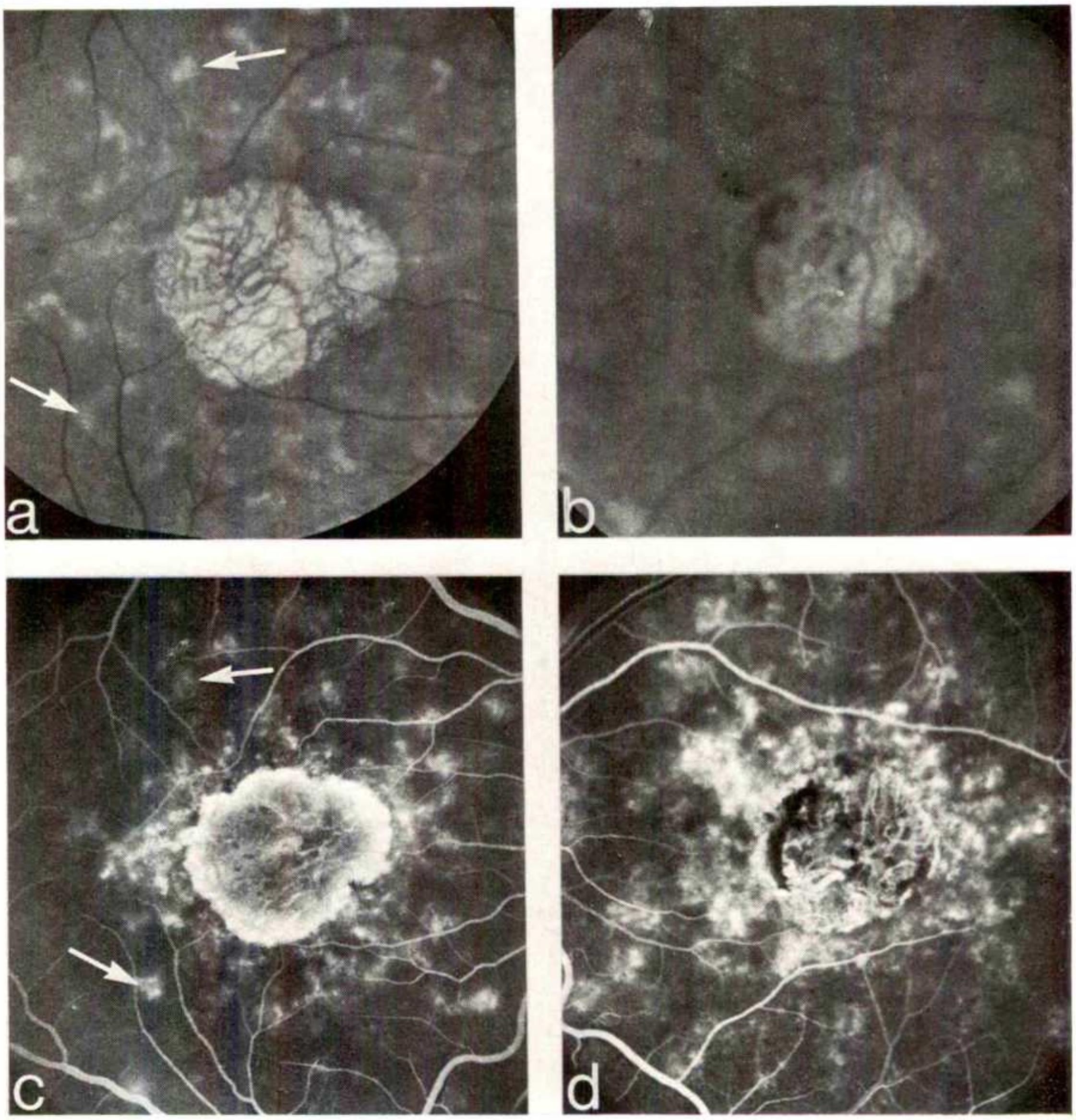

Fig. 6 *Case 4.* (a) *and* (b): *Fundus photographs of both eyes showed extensive pigment epithelial atrophy with visible large choroidal vessels. Note the white flecks at the level of the pigment epithelium* (arrows). (c) *and* (d): *Fluorescein angiograms of the lesions in* (a) *and* (b) *with loss of the choriocapillaris. The larger pigment epithelial flecks have hypofluorescent centres* (arrows)

with gradual loss of vision during the previous year. Prior to this he had 6/9 in both eyes with myopic glasses. *Visual acuities:* 6/18 right, 6/24 left. *Fundi:* typical bull's eye maculae (Fig. 9). *Fields:* bilateral paracentral scotomata; the field defect in the right eye was confined above the horizontal but in the left eye it extended downwards in a horseshoe pattern (Fig. 10). *Colour vision:* HRR plates showed a severe red-green deficiency and moderate blue-yellow deficiency: FM 100 hue testing was not possible. *Fluorescein angiography:* annular transmission defect in both eyes (Fig. 9). *Electrodiagnostic tests:* EOG: right 160%, left 190%. ERG: photopic reduced b-wave left eye; scotopic normal.

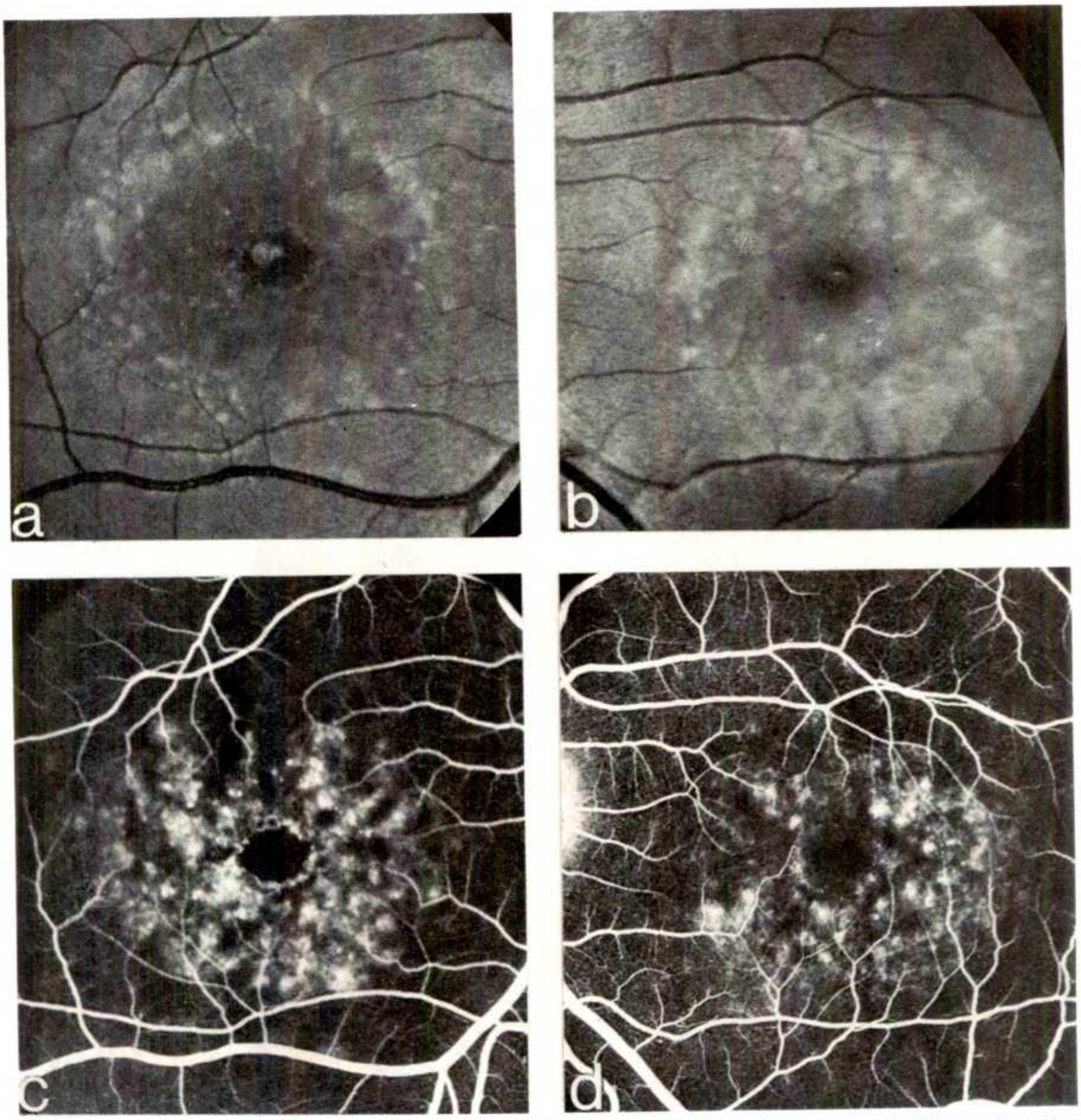

Fig. 7 *Case 5.* (a) *and* (b): *Atypical bull's eye maculopathy of both eyes with patchy pigment epithelial atrophy and white flecks in the pigment epithelium.* (c) *and* (d): *Fluorescein angiograms of* (a) *and* (b): *the larger flecks have hypofluorescent centres*

CFF: 60 right and left. VER: (46′ arc 20% contrast, 10 Hz) unrecordable in right eye and very small amplitudes in left eye (11·5′ arc 20% contrast, 10 Hz) amplitudes in both eyes rose to 1·2μv. *Heredity:* there was no family history of poor vision. His 2 sisters had normal acuities, colour vision, fundi, and fluorescein angiograms.

Follow-up: 12 months later he was reviewed. *Visual acuities:* 6/36 right, 6/60 left. *Fundi:* unchanged. *Fluorescein angiography:* unchanged.

CASE 7

A 23-year-old white woman in 1972 noticed difficulty playing tennis, as the ball disappeared when she was about to hit it. In October 1972 she was examined locally but no ocular defect was seen. Her

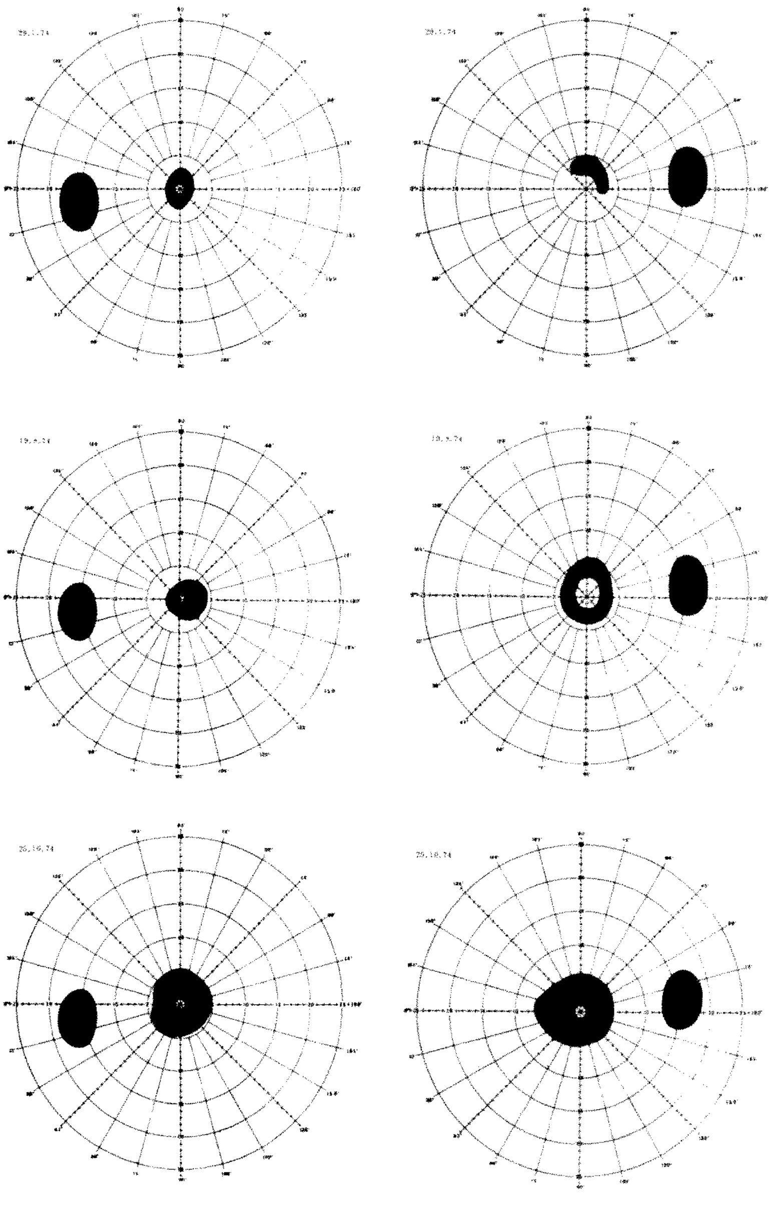

Fig. 8 *Case 5: serial fields of both eyes with 1/1000 white objects showing marked deterioration. There was little change in the visual acuities over the same period*

vision gradually deteriorated, and she was referred for further investigation in March 1974. *Visual acuities:* 6/9 in each eye. There was no refractive error. *Fundi:* typical bull's eye appearance (Fig. 11). *Fields:* annular defect from 1° to 4° from the fovea. *Colour vision:* HRR plates: mild red-green defect. *Fluorescein angiography:* annular transmission defect around the fovea (Fig. 11). *Electrodiagnostic tests:* EOG: 186% right, 190% left. ERG: photopic low amplitude b-waves in both eyes; scotopic normal. CFF: 40 right, 60 left. *Heredity:* she had no siblings; her parents had normal acuities and fundi.

Follow-up: the patient returned to Argentina, and further follow-up studies were not possible.

Results

The results are summarised in Table 1.

VISUAL ACUITY

All the patients studied except Case 4 had normal or

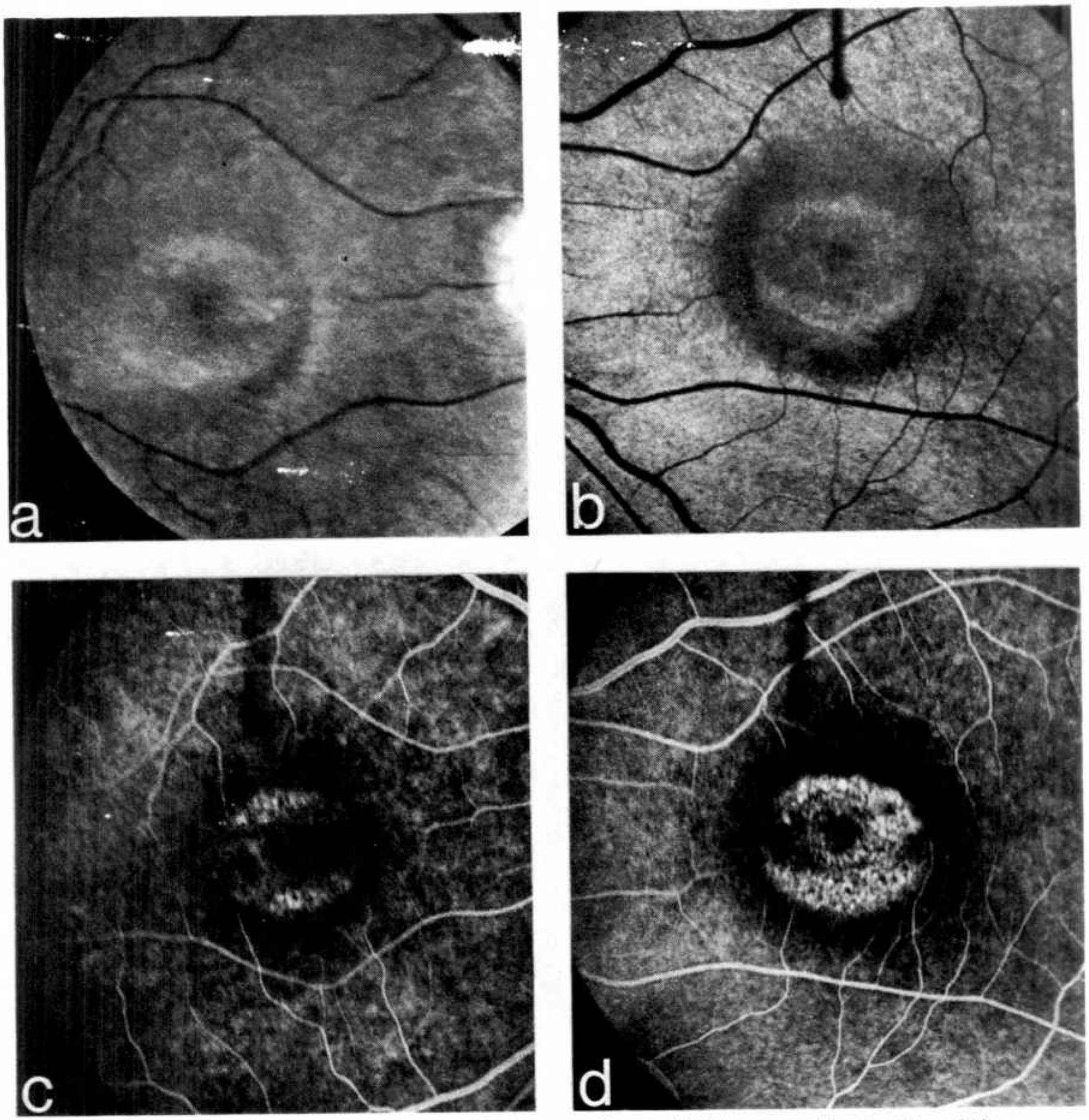

Fig. 9 *Case 6.* (a) *and* (b): *Fundus photographs of both eyes with typical bull's eye maculopathy.* (c) *and* (d): *Fluorescein angiograms of the same areas as* (a) *and* (b) *with hyperfluorescence corresponding closely to the pigment epithelial pallor*

near normal acuities when first seen. They showed deterioration of visual acuity during the period of follow-up, though the rate of visual loss was variable (Table 1). Case 3 showed minimal change over 3 years, whereas Case 6 had considerable worsening of acuity over 1 year. The remaining patients ranged between these extremes, although no follow-up was possible on Case 7.

The 2 patients with long-standing disease both had acuities of 6/60 but were able to carry out their occupations without difficulty. No patient had vision worse than 6/60 in either eye and some patients showed a moderate degree of asymmetry in the acuities of each eye.

Apart from Case 7 all the patients were myopic, although the greatest refractive error was −7·00

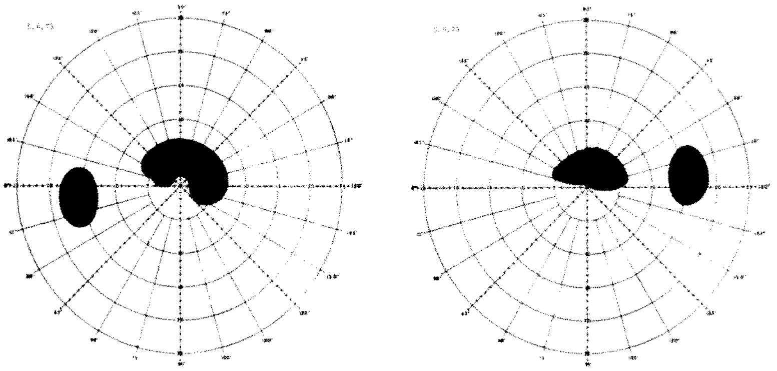

Fig. 10 *Case 6: paracentral scotomata in both eyes to 1/1000 white test objects*

dioptres, and none showed other signs of degenerative changes associated with myopia, nor did the degree of myopia change appreciably.

COLOUR VISION

Colour vision defects were present in all patients tested (Table 1). The Hardy Rand Rittler plates showed 3 patients to be almost achromatopsic, 1 patient to have severe red-green with moderate blue-yellow deficiency, and 2 patients with mild red-green deficiency. Only in 1 of these last patients (Case 3) was a Farnsworth Munsell 100 hue test possible. This produced a result indicative of a tritan defect rather than the protan or deutan defect suggested by the HRR plates. One patient with good visual acuity was not tested with the 100 hue test, but the remaining patients with a visual acuity good enough to perform the test found it impossible to carry out in any meaningful way as their hue discrimination was inadequate.

VISUAL FIELDS

The typical field defect found in these patients was a ring scotoma around central fixation. It extended from 1° out to 5° from the fovea and corresponded closely to the area of pigment epithelial change visible in the fundus. Cases 1 and 4, in whom the disease was longstanding, did not show these changes. Their visual acuities had fallen to 6/60 in each eye and a central area of sparing could not be demonstrated when specifically looked for. Case 6, who was also severely affected, did not have a ring scotoma. Both eyes had an upper paracentral defect, and in the left eye this extended down as if developing into an annular defect (Fig. 10).

Cases 2 and 3 had ring scotomata which remained static over the period of examination. Case 5 showed a progression of the ring scotoma (Fig. 8). During a 10-month period her visual acuity remained static at 6/12 in her right eye, although the field deteriorated. Her left eye showed a deterioration in both acuity and field.

No peripheral field defect was detected in any of the patients.

FUNDAL APPEARANCE

Five out of the 7 patients studied had similar fundal appearances with a normal or slightly darker than normal small central area surrounded by a lighter band. Around this lighter band was a further thin dark rim.

Two patients had atypical fundal lesions. Case 5 had a pigmented ring close to the fovea and white flecks in the pigment epithelium around the periphery of the macular area. Case 4 had a markedly different picture with an area similar to central areolar choroidal sclerosis at the fovea but white flecks in the pigment epithelium of the posterior pole similar to Case 5. During the period of observation the lesions appeared on ophthalmoscopy to change little, though the bull's eyes of Case 1 enlarged and Case 2 developed bull's eye lesions after 3 years.

FLUORESCEIN ANGIOGRAPHY

Fluorescein angiograms of the typical bull's eye lesions all showed a ring of hyperfluorescence corresponding closely to the paler zone on ophthalmoscopy. Of the 4 patients with serial angiograms 2 showed no appreciable change in the size of the lesions, 1 developed lesions during the period of observation, and the fourth showed a definite increase in the area involved and density of hyperfluorescence (Fig. 1). One patient showed typical transmission defects but had no serial photographs.

The 2 patients with atypical fundi showed other features. Case 5 showed pigment epithelial atrophy which was patchy over a large part of the macular area with a central hypofluorescent area. The large flecks visible on ophthalmoscopy were hypofluorescent centrally with hyperfluorescence at the

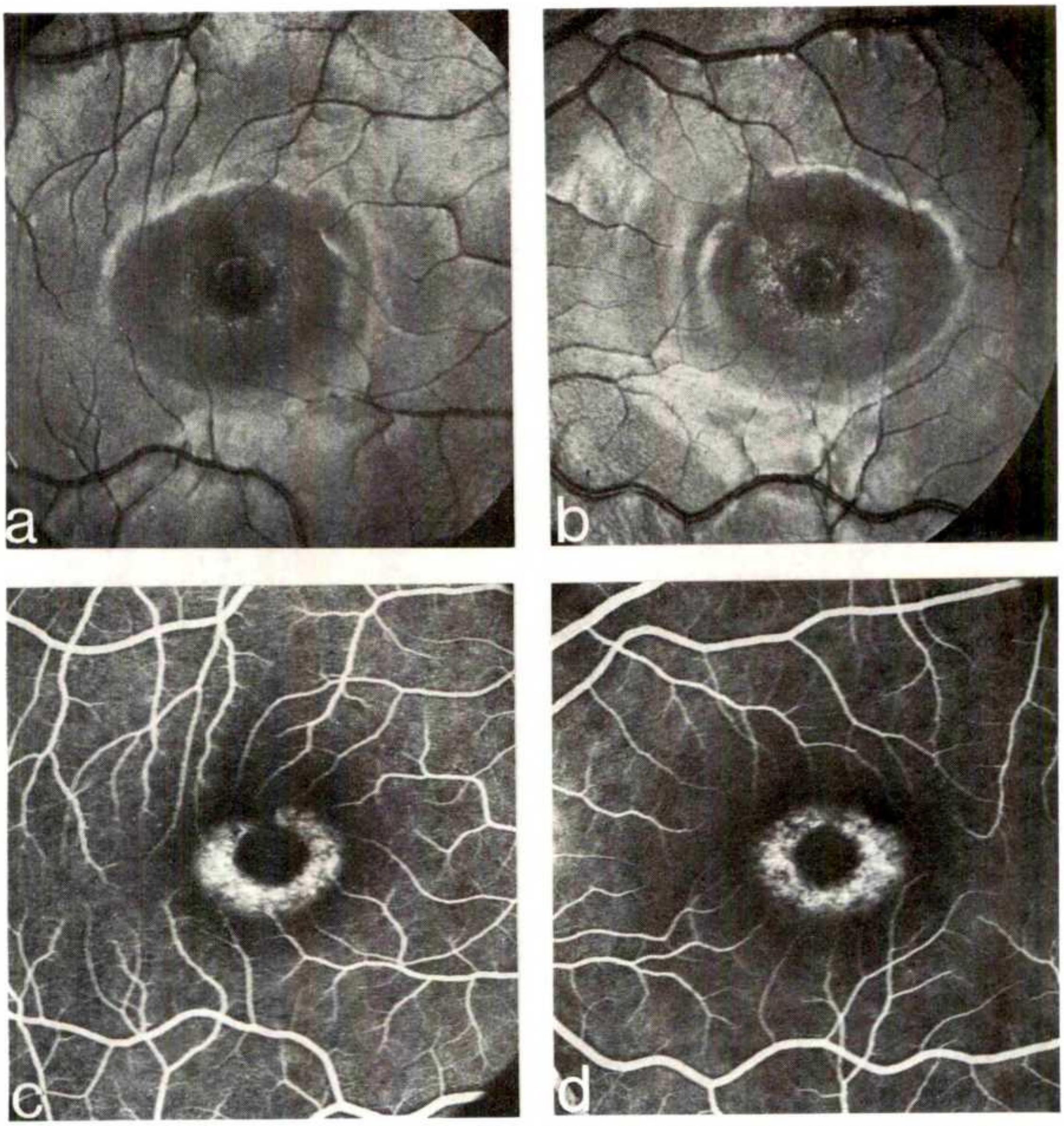

Fig. 11 *Case 7.* (a) *and* (b): *Fundus photographs with typical bull's eye maculae.* (c) *and* (d): *Fluorescein angiograms with annular transmission defects from the pigment epithelial atrophy*

edges. The small flecks were hyperfluorescent, with no central masking of the fluorescein. The appearance of the flecks changed little during the course of the angiogram but faded gradually as the background fluorescence faded.

Case 4 had marked loss of the central pigment epithelium and underlying choriocapillaris (Fig. 6). The larger choroidal vessels filled normally and did not appear to be grossly different from central areolar choroidal sclerosis. The white flecks in the pigment epithelium had the same characteristics as those in Case 5.

ELECTRODIAGNOSTIC TESTS

Electro-oculogram

The EOG was normal in all the patients with a

Table 1

Case	*Age*	*Sex*	*Refraction*	*VA first recorded*	*VA final*	*Colour vision*	*Field*	*Fundus*
1	35	M	R: –4·00/–3·00 L: –3·75/–2·00	R: 6/6 L: 6/6	R: 6/60 L: 6/60	Achromat	Central scotoma	BE
2	28	M	R: –1·50 DS L: –1·50 DS	R: 6/9 L: 6/9	R: 6/18 L: 6/24	Strong R-G and moderate B-Y defects	Ring scotoma 2°–4°	N
3	37	M	R: –4·00/–0·75 L: –4·00/–0·75	R: 6/9 L: 6/6	R: 6/12 L: 6/9	Mild R-G and ? B-Y defects	Ring scotoma 1°–5°	BE
4	46	M	R: –2·00/–1·00 L: –1·50 DS	R: 6/60 L: 6/60	R: 6/60 L: 6/60	ND	Central scotoma	Choroidal atrophy with PE flecks
5	25	F	R: –0·50 L: –0·50	R: 6/12 L: 6/6	R: 6/12 L: 6/24	Achromat	Paracentral scotoma/ Ring scotoma	A typical BE with PE flecks
6	28	M	R: –2·75/–2·50 L: –3·50/–0·75	R: 6/9 L: 6/9	R: 6/24 L: 6/60	Achromat	Paracentral scotoma	BE
7	22	F	R: Emmetropic L: Emmetropic	R: 6/9 L: 6/9	—	Mild R-G defect	Ring scotoma 1°–4°	BE

BE = Bulls eye. D = Dominant. ND = Not done. R-G = Red/green. SN = Subnormal. B-Y = Blue/yellow.

typical bull's eye fundus. The two atypical patients with flecks had an EOG moderately reduced to 155–160% light rise.

Electroretinogram

The scotopic ERG was normal in all patients.

The photopic ERG had a reduced b-wave in all the patients tested apart from Case 3, who was the most mildly affected patient in the series. The a-waves were unaffected even in those patients who had had the disease many years.

Critical fusion frequency

The CFF showed a more variable pattern. Three patients had a normal CFF in both eyes and another patient had a normal CFF in 1 eye. Case 5, with the atypical fundal appearance, had a CFF of 16 in each eye. Case 2 had a CFF of 40 in each eye at a time when his fundi appeared normal, although his vision later deteriorated to 6/18 right, 6/24 left.

Visually evoked response

The pattern VER showed a severe reduction in the amplitude of the wave recordings in all the patients tested. Case 6 was found to have higher amplitudes when the square size was reduced from 46′ arc to 11·5′ arc, though they still remained very low. The increased number of edges from the smaller squares which crossed the centrally spared area of the macula would account for this heightened response. Two patients had a flash VER. Case 3 had reduced amplitudes and a marked delay in the conduction time to the cortex (220 ms right eye and 250 ms left eye) This could not be explained, especially as he was the least severely affected patient in the series. Case 4 had mildly reduced amplitudes. Case 5, with the atypical bull's eye lesions, showed a reduced response, but when only the central areas were tested the amplitudes fell to unrecordable levels.

GENETICS

Two patients had dominant inheritance with very different clinical and electrophysiological manifestations. Case 3 had bull's eyes maculae with mild colour and electrophysiological disturbances, whereas Case 4 had marked macular atrophy.

Although there was no history of consanguinity, the remaining patients were considered to be either recessive or sporadic cases. No affected relatives were found and there was no family history of visual loss. Within this group of 5 patients the progress of the cone loss was very variable; 1 had a slow deterioration over 13 years, 1 had a gradual loss over 3 years, and 2 had more rapid involvement over 1 to 2 years.

Discussion

VISION

Visual acuity

The majority of the patients form a distinct entity with a presenting symptom of visual loss, although the visual acuity may be normal or near normal on testing with a Snellen chart. Later the central vision may be reduced to 6/60, but this is not invariable, and deterioration may take many years.

Most published series of cone degeneration do not have follow-up information, but the results here

Fluorescein angiography	*EOG*	*Photopic ERG*	*Scotopic ERG*	*CFF*	*VER*	*H*	*Follow-up*	*Progress*
Ring transmission	N	SN b-wave	N	N	Low ampl.	R/S	Increase in size of BE (Fig. 1)	Slow deterioration over 13 years
N	N	SN b-wave	N	Reduced	Low ampl.	R/S	Developed BE lesion (Fig. 2)	Moderate deterioration over 3 years
Ring transmission	N	N	N	N	Low ampl. delayed	D	Mild colour deterioration 100 hue (Fig. 5)	Mild deterioration over 3 years
Atrophy of chorio-capillaris Patchy transmission	SN	ND	ND	ND	Low ampl.	D	Static	Severe deterioration many years previously
Central hypo-fluorescence Patchy transmission	SN	SN b-wave	N	Very reduced	Low ampl.	R/S	Increase in area of field loss (Fig. 8)	Moderate loss over 1 year
Ring transmission	R: SN L: N	R: N L: Sl. SN b-wave	N	N	Low ampl.	R/S	No apparent change in retinae	Severe deterioration over 2 years
Ring transmission	N	Sl. SN b-wave	N	R: reduced L: N	ND	R/S	No follow-up	No follow-up

N = Normal. PE = Pigment epithelium. R/S = Recessive/sporadic. H = Inheritance

broadly agree with those of Krill *et al.* (1973), although they had no case of bull's eye maculopathy with vision better than 6/12. They found that the rate of visual loss varied greatly from patient to patient and that the final acuity often remained at 6/60. There was also a moderate degree of asymmetry between the acuities of the 2 eyes as found with this series. They also suggested that younger patients tend to be more severely affected than those in whom the disease becomes manifest later in life. This idea would be borne out by this series, though all the patients developed symptoms between the ages of 22 and 35 years apart from Case 4. He was affected at the age of 12 and showed greater macular atrophy than the others. It is interesting that his brother did not have symptoms until the age of 35, and he was less affected than the other patients. They presumably had a dominantly inherited disease, but their clinical appearances and visual functions were very different.

None of the patients had nystagmus, and only 1 patient had symptoms of photophobia. Both nystagmus and photophobia are well recognised accompaniments of cone disfunction although by no means consistently found (Goodman *et al.*, 1963; Kelsey and Arden, 1972).

Colour vision

In degenerative conditions of the cone photoreceptors abnormalities of colour vision are usually present and invariably so in the cone disfunctions. Few of the patients in this series were initially aware of this abnormality until tested. However, in Case 2 colour loss was his original symptom and it preceded any loss of visual acuity or visual field by 2 to 3 years. Previously reported series in which colour vision has been assessed do not seem to have had similar difficulty with the 100 hue test as experienced by us. Even though the acuities of some of our patients were good their colour vision was severely affected as shown by the relatively crude HRR plates.

Visual fields

An annular field defect was demonstrated in 4 patients and paracentral scotomata were found in another. It is conceivable that the remaining 2 patients may have had similar field defects if they had been seen earlier in the course of their disease and they had been specifically looked for.

Annular field defects have been noted previously with cone dystropies (Sloan and Brown, 1962; Krill *et al.*, 1973; Yokoyama *et al.*, 1974), and resemble those of chloroquine retinopathy (Okun *et al.*, 1963; Kearns and Hollenhorst, 1966). Sparing of the foveal cones with preservation of good visual acuity and more severe loss of perifoveal cones could account for the ring field defect. Goodman *et al.* (1963) found no demonstrable field defect in the majority of their patients tested, but only one had a bull's eye macula.

RETINAL MORPHOLOGY

The typical fundus appearance of a bull's eye pigmentary abnormality with a corresponding ring transmission defect on fluorescein angiography was present in 5 of the patients. This appearance resembles chloroquine retinopathy but is usually more localised. Chloroquine toxicity is the most widely recognised cause of bull's eye maculopathy, and cases have been described with annular field defects and sparing of the central vision (Okun *et al.*, 1963; Kearns and Hollenhorst, 1966). However, chloroquine retinopathy does not produce a specific b-wave loss in the ERG, and both the ERG and EOG may be affected independently. The bull's eye itself is often larger with more diffuse changes in the pigment epithelium on fluorescein angiography. Siegel and Smith (1967) described a case of non-progressive bull's eye maculopathy and ring scotoma following drug toxicity which was not due to chloroquine, but most other toxic retinopathies do not produce a bull's eye lesion. Case 2 had received chloroquine for malaria but the total dose (5 g) was well below that normally associated with macular degeneration and his colour vision loss preceded the onset of malaria.

Other causes of bull's eye maculopathy are less common. Weise and Yannuzzi (1974) reported 9 patients who had annular transmission defects on fluorescein angiography. Although they did not perform colour vision testing or electrodiagnostic studies, their cases included central serous retinopathy, fundus flavimaculatus, Stargardt's juvenile macular degeneration, and senile predisciform changes of the pigment epithelium.

Chopdar (1976) described a case of bull's eye maculopathy in a woman with peripheral vascular closure of the retina. He did not link the 2 abnormalities, and the electrophysiology and colour vision showed the macular changes were not due to cone dysfunction.

ELECTROPHYSIOLOGY

The normal scotopic ERG indicated that either the abnormality was confined to the cones or that the macular area only was involved (Merin and Auerbach, 1970). On electrodiagnostic testing the loss of the photopic b-wave and markedly diminished VER appeared to be a consistent finding. The ERG abnormalities suggested widespread cone loss and that the rods were intact. Sparing of the a-wave and involvement of the b-wave is difficult to explain, although it has been noted previously by Yokoyama *et al.* (1974). Although a normal photopic ERG is against the diagnosis of cone dysfunction, Case 3 had the other criteria of this disorder and had affected relatives. Four of the 24 bull's eye patients of Krill also had normal photopic electro-retinograms.

The photopic ERG and CFF indicate the degree of cone involvement in the whole retina, but it may be from these results that the photopic ERG is a more sensitive indicator of cone abnormality in this disorder than CFF levels.

Cases 4 and 5 had a more generalised pigment epithelial disease than the other 5 patients, which accounts for the flecks and reduced EOG. Krill *et al.* (1973) found a reduced EOG in 12 of their 24 patients with a bull's eye appearance and cone dystrophy, and Kelsey and Arden (1972) found an abnormal EOG in 9 of their 13 patients with cone dysfunction.

Abnormalities of the VER have not been described previously in cone dysfunction in any detail, presumably because the macular involvement has been assumed always to affect the response. In this series the degree of involvement seemed out of proportion to the loss of foveal cones, as 4 of the patients had 6/9 vision or better in at least 1 eye when tested. The pattern VER, which reflects the macular function, would be expected to have near normal amplitudes with good visual acuity. The reduced flash VER response was a further indication of the generalised nature of the receptor dystrophy.

GENETICS

Dominant, recessive, and X-linked inheritance have been described with acquired cone dystrophies (Goodman *et al.*, 1963; Berson *et al.*, 1968a; Davis and Hollenhorst, 1955; Krill and Deutman, 1972; Pearlman *et al.*, 1974). None of our patients showed X-linked inheritance, which according to Goodman *et al.* (1963), tends to be manifest in children and become static early in life.

The 2 related patients had dominant inheritance and showed markedly different fundal pictures. Such a degree of variation is unusual, although Steinmetz *et al.* (1956) examined a dominant family of 158 members and found that one branch developed pigment granularity of the fovea and another branch developed choroidal atrophy. Similar disparity was also previously noted with dominant inheritance in cone dystrophies by Sloan and Brown (1962) and by Krill *et al.* (1973) and is also a well-recognised feature of other dominantly inherited disorders.

As with dominant inheritance, Krill *et al.* (1973) showed that recessive inheritance also has a variable picture, and different affected members of the same family may have different clinical manifestations.

Krill and Deutman (1972) reported 2 families with several members with bull's eye maculae which they believed to be cone degenerations. As well as the typical features several of their patients also had an abnormal EOG and scotopic ERG. Deutman (1974) described a macular disorder of similar appearance inherited as a dominant disease which he called benign concentric annular macular dystrophy. Although this may have a bull's eye appearance, the visual acuity and colour vision are only mildly affected, and the scotopic ERG may be reduced as well as the photopic ERG and the EOG. As he pointed out, some of these patients had rod involvement as well as cone involvement.

Hittner *et al.* (1975) showed that cone-rod degeneration may initially produce a bull's eye maculopathy and be inherited as a dominant condition. However, their patients progressed and some lost all vision with loss of EOG, photopic and scotopic ERG, and had pigmentary changes in the retinal periphery.

AETIOLOGY

The aetiology of cone degeneration is unknown and may be different in different patients. Dominant and recessive inheritance may be responsible for 2 different types of cone loss even though the clinical manifestations are similar. On the other hand the 2 related patients of this series, who presumably had the same dominantly inherited condition, showed very different clinical pictures, indicating that environmental or constitutional factors must also be relevant to the disease severity. A bull's eye macula with good visual acuity does not necessarily indicate that the cone degeneration is in an early stage, although this may be the case. Also, there may be serious cone malfunction with severe visual and electrophysiological abnormalities with normal fundal appearance (Berson *et al.*, 1968a; Krill *et al.*, 1973; Ohba, 1974).

Diffuse cone loss was probably present in most if not all the present series judging by the abnormal photopic b-waves, but why this should produce a bull's eye appearance is difficult to explain. The photoreceptors and pigment epithelium behave as a functional unit, and diseases of one affect the other as in vitamin A deficiency, retinitis pigmentosa, and myopia. Central pigment epithelial change might be expected to follow cone degeneration as the rod population of the macula is less dense, and conversely the peripheral pigment epithelium would be expected to be relatively normal where the cone population is much less numerous. The central island of more normal pigment epithelium may suggest that there is some overall cone survival, and on account of the high density of cones at the fovea there are sufficient viable receptors to maintain a normal pigment epithelium. This may also explain the relatively good visual acuity, as it is known that loss of half the foveal vision is compatible with normal acuity.

Conclusion

Some patients with acquired cone degeneration may present with clearly identifiable signs, although the visual acuity is good at least in the initial stages. The presence of marked colour deficiency, bull's eye maculae, and perifoveal annular scotomata should suggest the diagnosis. This may be confirmed by loss of the photopic element of the ERG and a disproportionately affected VER. Other disorders of the receptors and pigment epithelium may produce a similar clinical picture, but electrodiagnostic testing, the clinical progression of the disease, and the age of the patient should help in the differential diagnosis and the identification of pure cone loss.

The patients described in this report have the features of pure cone degeneration. The rod functions appeared to be normal both symptomatically and on electrodiagnostic testing, and there was no pigmentary abnormality in the peripheral fundus as described by Berson *et al.* (1968b) and by Hittner *et al.* (1975).

It would seem, from reviewing these patients and previously described reports, that cone dystrophy may have different aetiologies and that the clinical manifestations may vary within each aetiological group. Further breakdown of the cone dystrophies into different groups may depend on identification of specific biochemical defects.

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An unusual presentation of Best's disease

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SUMMARY We diagnosed an unusual case of Best's disease in a patient with multiple geographic macular and extramacular lesions. Initial confusion in the diagnosis arose because of a past history of intravenous drug abuse by the patient. The electro-oculogram was helpful in establishing the correct diagnosis.

Best's hereditary macular degeneration (vitelliform macular dystrophy) was first described in 1905 (Best, 1905). Although most ophthalmologists have a mental image of a 'sunny-side-up egg' becoming a 'scrambled egg', Best's disease may be difficult to recognise clinically. At times extramacular, atypical macular, or multiple lesions may be present (Miller, 1977). We here describe a patient with multiple atypical macular and extramacular lesions in whom a definitive diagnosis was not made until electrophysiological testing was performed.

Case report

A 19-year-old white man first noted blurred vision in February 1975. He was first seen by an ophthalmologist in August 1975. Visual acuity at that time was 20/20 in the right eye and 20/25-3 in the left eye. Multiple globular subretinal exudates, primarily located superiorly, were described in the posterior poles of both eyes. No diagnosis was made.

The patient's past medical history revealed intravenous drug abuse (cocaine, heroin, and barbiturates) from October 1974 until April 1975 and chronic active hepatitis confirmed by liver biopsy. He was, however, asymptomatic except for his eyes. There was no known history of familial ocular disease.

The patient was next seen in February 1976. His visual acuity was 20/20 in both eyes. The ophthalmoscopic appearance at this time was described as a circinate pattern of deep retinal exudates in the posterior poles of both eyes. It was considered possible that the eye findings were somehow related to his past history of drug abuse. The patient's ocular examination, however, remained unchanged during the next month, and he was transferred to the Walter Reed Army Medical Center for further evaluation.

We first saw the patient on 18 March 1976. Visual acuity was 20/20 bilaterally. Results of slit-lamp biomicroscopy and applanation tonometry were normal. Dilated examination of the fundus showed bilateral, multiple, discrete, and confluent geographic yellowish lesions in either the deep retina or in the pigment epithelium (Figs. 1–3). Goldman perimetry showed bilateral relative paracentral scotomas. Fluorescein angiography disclosed blocking of the choroidal fluorescence by the lesions (Fig. 4). Electroretinography, dark adaptometry, and colour vision testing were all normal. Electro-oculography showed a light-peak to dark-trough ratio of 1·35 in the right eye and 1·23 in the left eye (normal is greater than 1·65). A definite diagnosis of Best's disease was made.

Discussion

Best's hereditary macular degeneration is a well-described entity but is sufficiently uncommon in clinical practice to cause confusion in diagnosis. The ophthalmoscopic appearance may include a normal fovea, vitelliform lesions, macular cysts, pseudohypopyons, or chorioretinal atrophy (Falls, 1969; Maloney *et al.*, 1977). The lesions may be bilateral or unilateral, single or multiple, macular or eccentric (Falls, 1969; Miller, 1977).

The inheritance of Best's disease is thought to be autosomal dominant with variable penetrance and expressivity (Deutman, 1971). The age range of the patients at the time of presentation varies from

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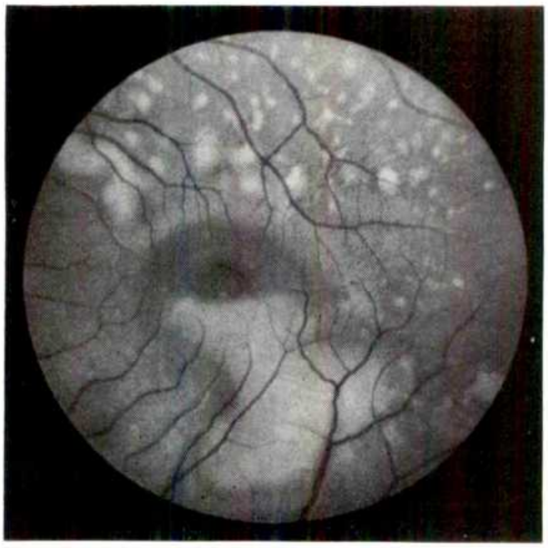

Fig. 1 *Posterior pole of left eye showing pseudohypopyon in a large geographic lesion and multiple smaller lesions*

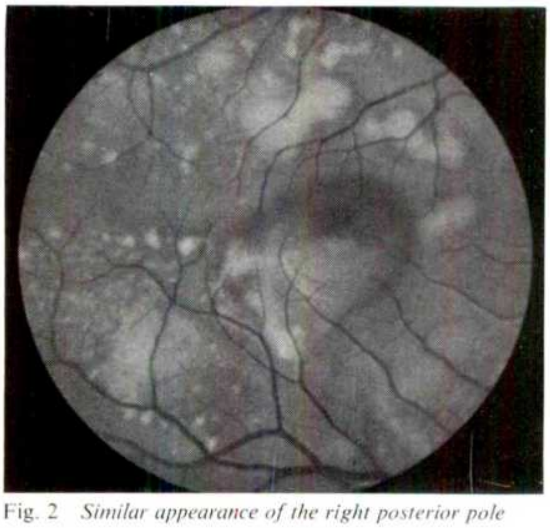

Fig. 2 *Similar appearance of the right posterior pole*

1 week to 74 years (Deutman, 1971). Because the penetrance and expressivity may be variable, a patient who has an atypical lesion may be unaware of other family members similarly affected, and, therefore, will not provide the examiner with this potentially valuable clue. The electroretinogram and dark adaptation findings are often normal (Fishman, 1975). Colour vision may be mildly or markedly abnormal, the degree depending on the extent of the macular damage (Krill and Archer, 1977). Fluorescein angiography discloses blockage of choroidal fluorescence by the lesion, which is not characteristic enough to lead to a definitive diagnosis. Fluorescein studies have shown in some cases a choroidal neovascular membrane within the ruptured vitelliform lesion (Miller *et al.*, 1976). The electro-oculogram, with few exceptions, is subnormal and it can be helpful in diagnosing apparently normal carriers, subtle early cases, or, as in our patient, atypical presentations.

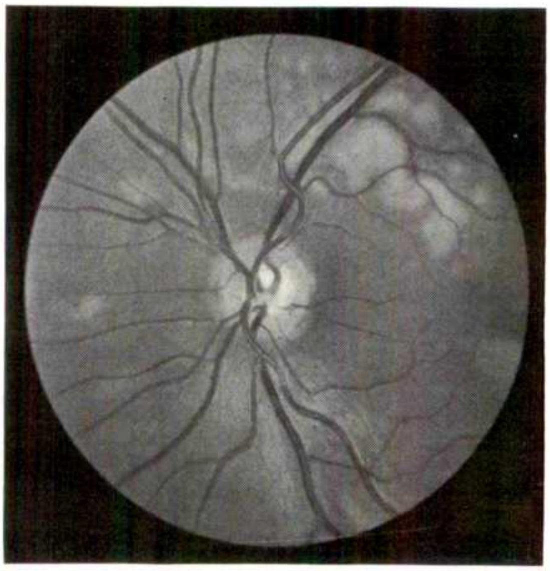

Fig. 3 *Peripapillary area of the left eye showing nasal location of some of the lesions as well as macular involvement*

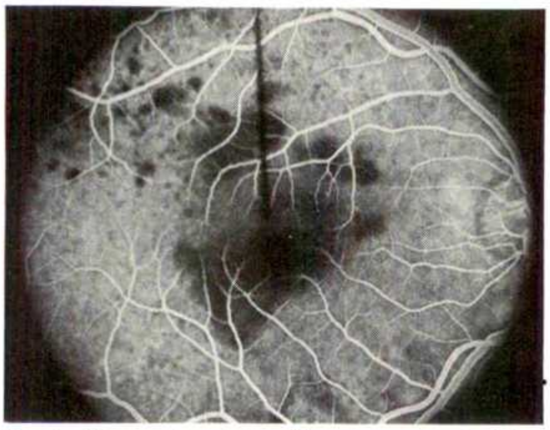

Fig. 4 *Fluorescein angiogram (late venous phase) of the right eye showing blocked choroidal fluorescence corresponding to some of the lesions. Other fainter lesions do not block the choroidal fluorescence*

We thank Ken Kramer, MD, who performed the electrophysiological testing, and Ellen Foer, who performed the photography.

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An improved objective slit-lamp fluorophotometer using tungsten-halogen lamp excitation and synchronous detection

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SUMMARY A new design of fluorophotometer is described. The instrument can measure lower concentrations of fluorescent dye with greater accuracy than previous models.

Fluorophotometry, in ophthalmology, is the investigation of fluid exchange in the various transparent structures of the eye by the non-traumatic measurement of the rate of change of concentration of an innocuous fluorescent dye (usually sodium fluorescein) that has been introduced into the eye. The fluorescence is excited and observed by means of an optical system which is similar in design to a slit-lamp microscope but with provision for measuring the intensity of the fluorescent light collected.

Langham and Wybar (1953, 1954) built the first truly objective fluorophotometer which employed a photomultiplier tube (PMT) to measure the intensity of the fluorescent light. Maurice (1963) completely redesigned their instrument, making several important advances. In particular, a clear indication of the position within the eye of the small volume from which fluorescent light was being collected enabled the measurement of fluorescein concentration to be achieved for the first time within structures of the eye other than the relatively bulky aqueous humour. This and Maurice's other new features are incorporated into the present instrument.

Developments since Maurice's instrument have included an attachment designed by Waltman and Kaufman (1970) to allow the conversion of conventional slit lamps into objective fluorophotometers. This attachment, which includes a fibreoptic probe, does not enable discrimination against ambient light to be made. Bloom *et al.* (1976) have redesigned the electronics of Maurice's instrument and have eliminated any significant instability due to variations in mains frequency by employing synchronous detection. However, they still employ mercury arc excitation, which is inherently unstable, and in practice their instrument is not capable of measuring accurately to as low a concentration as the fluorophotometer described here.

Design

The layout of the present instrument is shown in Fig. 1. A tungsten-halogen light source driven from a stabilised power supply is used. The optics of the lamp are similar to those of a conventional slit lamp except that the light beam is chopped at 1 kHz by means of a motor-driven disc with 100 slots. The light beam is filtered by a Baird Atomic B4 interference filter F_1, which passes blue light in the wavelength range 440 nm to 500 nm. The projected image of the slit S_1 within the subject's eye is approximately 200 μm by 600 μm.

The monocular microscope gives an upright image for convenience. A portion of the band of fluorescent light which appears in the microscope field of view is selected by means of a window W in the mirror M_1 which is situated at an intermediate image plane in the microscope and is therefore visible to the operator. Before being allowed to impinge on the PMT photocathode the light so selected is passed through a coloured glass filter F_2 (Barr and Stroud OG15) which passes visible wavelengths longer than 515 nm and hence rejects any scattered blue excitation. The projection of the window W through the microscope objective O_2 produces an image approximately 400 μm wide and 1,400 μm high within the subject's eye which serves to define the region from which fluorescent light can be collected and registered by the detection system.

Since the light exciting the fluorescence is modu-

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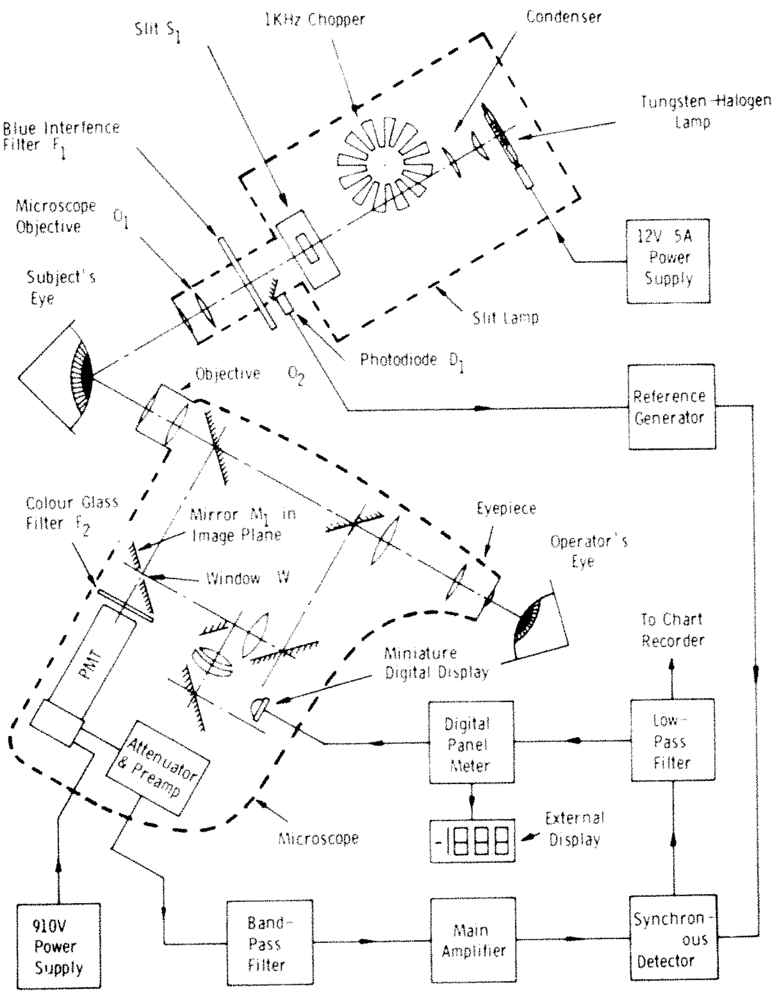

Fig. 1 *Layout of the instrument. The slit lamp, in which the light is chopped at 1 kHz, is at the top of the diagram. The microscope housing, which also contains the photomultiplier tube and its associated attenuator and preamplifier, is shown beneath this*

lated, an alternating current signal appears at the PMT anode, thus allowing it to be separated from any direct-current components due to ambient light or PMT dark current. This signal is synchronously detected, the reference being derived from the output of photodiode D_1, which is illuminated by the chopped incident beam, and then low-pass filtered to reduce fluctuations due to the inherent shot noise from the PMT; provision is also made for three possible filter time constants. The output may either be displayed on a chart recorder or observed on the built-in digital panel meter (DPM). One digital display from this meter is visible in the field of view of the microscope for convenience while a second display is located on the instrument's top panel. Also provided are a preset offset control, which need be adjusted only at the beginning of an experiment, and a control to vary the gain from its normal calibrated value.

Performance

The linearity of the instrument is shown in Fig. 2. These measurements were obtained by using a series of dilutions of sodium fluorescein in tap water (about pH 8·0) made up the same day in small stoppered test tubes and were achieved without the use of neutral density filters. A single attenuator switch enables accurate measurement of concentrations throughout the linear range from 2×10^{-9} g ml^{-1} to 2×10^{-5} g ml^{-1}, with the results displayed to three significant figures by the DPM. This performance is achieved with the fluorescent light collected from a small volume of height 600 μm, depth 200 μm, and width 400μm, as defined by the intersection of the excitation beam with the projection of the window W through the microscope objective O_2.

The use of modern integrated circuit technology, stabilised power supplies, and a tungsten-halogen lamp has resulted in a compact design (Fig. 3), with less than 3% change in sensitivity for mains voltage variations in the range 200 to 260V and less than 2% of full scale drift measured over 1 hour (after a 20-minute warm-up period). The use of a synchronous detection system results in less than 3% change in sensitivity for a ±8% change in mains frequency. Careful design has resulted in only 6 dB of noise being introduced by the photomultiplier, preamplifier, and detection system.

Absolute fluorescein concentrations in the larger transparent media of the eye can be measured by first calibrating the instrument against a standard solution (usually 1×10^{-6} g ml^{-1}) held in a test tube.

Preliminary clinical trial

Clinical studies have confirmed that the instrument is capable of measuring tear film fluorescein concentration over relatively long periods of time in order to estimate tear flow rate. Moreover, the sensitivity range of the instrument is compatible with the measurement of fluorescein concentration not only in the precorneal film but also in the clear ocular media (Maurice, 1967), thus allowing measurement of aqueous flow rate and changes in the diffusion barriers within the eye in a wide range of conditions.

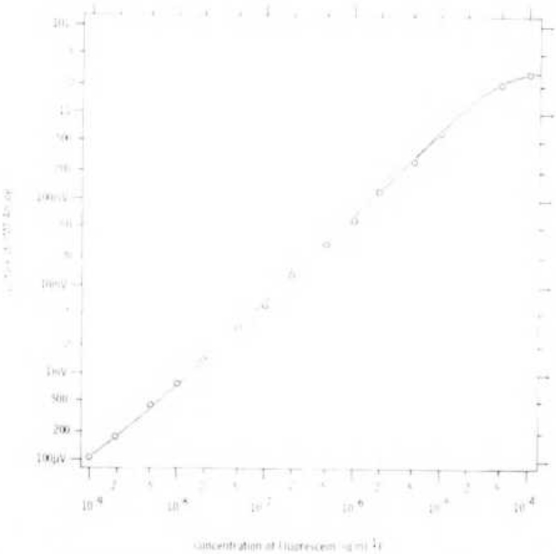

Fig. 2 *Response of the instrument to different fluorescein concentrations. This plot of PMT anode voltage versus fluorescein concentration on logarithmic scales was obtained by using successive serial dilutions of sodium fluorescein contained in small stoppered test tubes. The range of practically linear response is from* 2×10^{-9} *g ml*$^{-1}$ *to* 2×10^{-5} *g ml*$^{-1}$

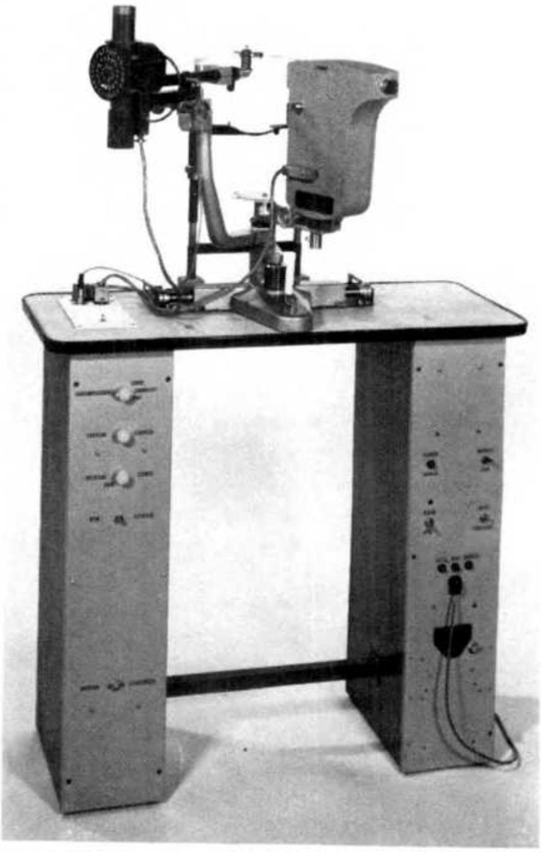

Fig. 3 *The complete instrument. The microscope and slit lamp are mounted on the two arms of the slit lamp manipulator. The supporting cabinet contains electronic circuitry for the detection system and the power supplies*

Conclusions

By using a tungsten-halogen lamp and a synchronous detection system in the design of the present fluorophotometer two sources of instability in previous instruments have been eliminated and the performance has been improved; the whole of the useful range of fluorescein concentrations, from about 2×10^{-9} g ml^{-1} to 2×10^{-5} g ml^{-1}, can be measured without the need for neutral density filters. Furthermore, owing to the extensive use of integrated circuits, the amplification and detection system of the final instrument is compact and relatively cheap. In a preliminary clinical trial the instrument was found to be convenient and simple to use for measuring fluorescein concentration in the precorneal tear film.

Dr D. Maurice and Mr W. Buchanan were involved in the early stages of the development of this fluorophotometer, and have given much helpful advice.

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A cannulated probe for torn inferior canaliculus repair

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SUMMARY A cannulated probe and silicone tube for the repair of the torn inferior canaliculus are described and illustrated.

The repair of the torn inferior canaliculus (Fig. 1 *a* and *b*) remains one of the ophthalmic surgeon's more tantalising problems, to which many approaches have been made. Among these are an ingenious method devised by D. P. Greaves (Stallard, 1976), using a lachrymal cannula and nylon thread, the retrograde needles of Kellnar (1960), the hooked pigtail probe from the Dutch Medical Workshop (Worst, 1962), the French eye pigtail probe (Kartch, 1971), and a method devised by Meacham (Meacham, 1972), using the Veirs rod (Veirs, 1962) and the pigtail probe (Worst, 1962).

The author has developed the lachrymal cannula a stage further and designed a cannulated probe (Fig. 2) with left and right-sided ends. Having introduced this instrument via the upper punctum and canaliculus until it presents at the torn medial end of the lower canaliculus or at the orifice of the lower punctum (Fig. 3), a length of silicone tubing, fused to a 4/0 nylon suture (Fig. 4) (Caudwell-Docherty tube), is introduced into the probe (Fig. 5). It can be seen that when the silicone is homed into the tip of the probe (Fig. 6) the transition from probe to tubing is smooth and atraumatic to the delicate epithelium of the canaliculus. The probe is then withdrawn (Fig. 7).

Silicone tubing is the ideal material for intubation as it is sufficiently wide to re-establish the original canaliculus's internal diameter and, being flexible, is well tolerated strapped to the forehead for 4 weeks. It therefore increases the probability of successful reconstruction of the canaliculus.

The operating microscope and constant suction greatly facilitate the introduction and passage of the probe into the canalicular circuit, as the tip can often be observed throughout its passage along the canaliculae.

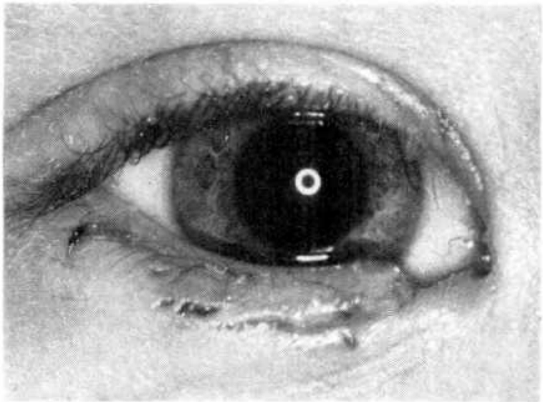

Fig. 1*a* *Torn inferior canaliculus*

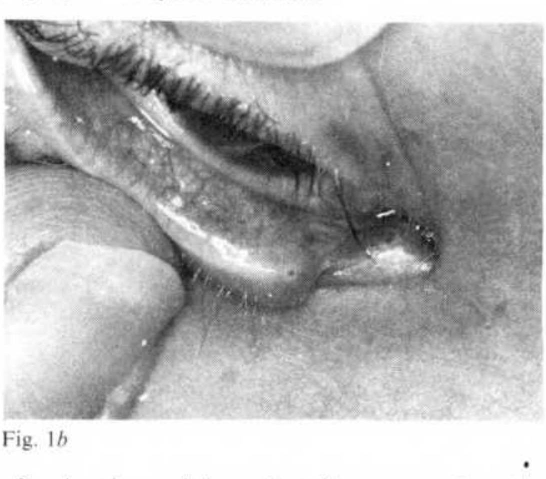

Fig. 1*b*

Where the injury is restricted to the tissues near the torn canaliculus, 6/0 collagen has been found most suitable for repairing both the subcutaneous

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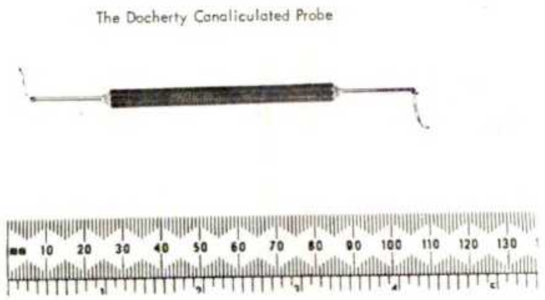
The Docherty Canaliculated Probe
mm 10 20 30 40 50 60 70 80 90 100 110 120 130

Fig. 2 *The Docherty cannulated probe*

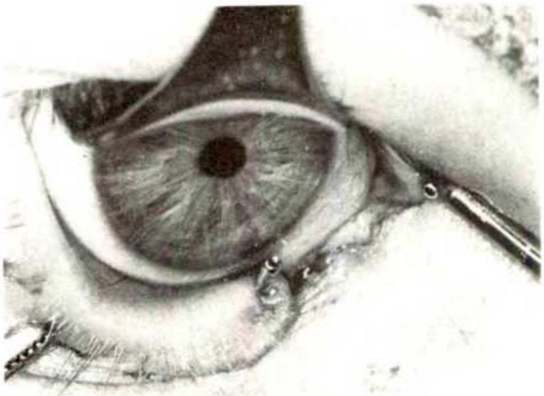

Fig. 3 *Probe presenting at the lower punctum*

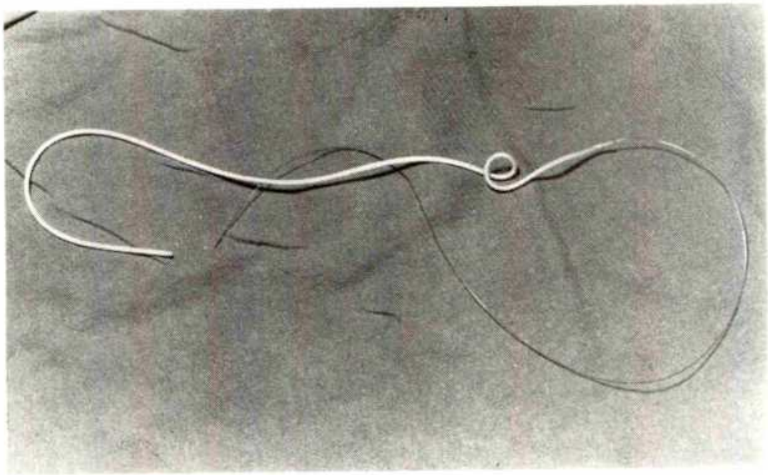

Fig. 4 *The Caudwell-Docherty tube in the probe*

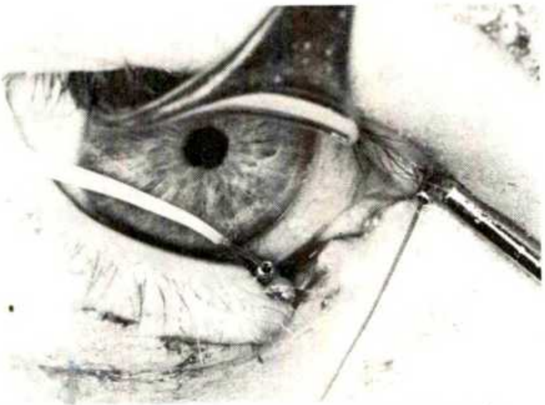

Fig. 5 *Nylon portion of the Caudwell-Docherty tube in the probe*

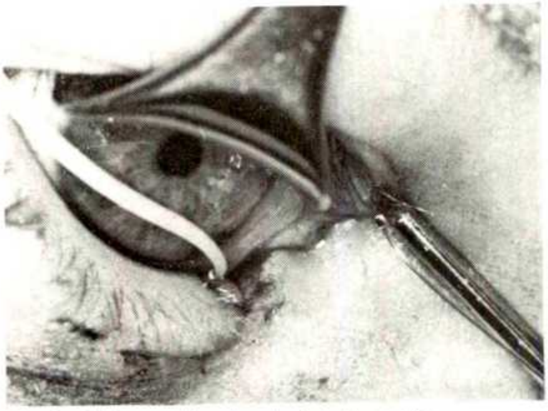

Fig. 6 *Silicone tubing homing into the probe*

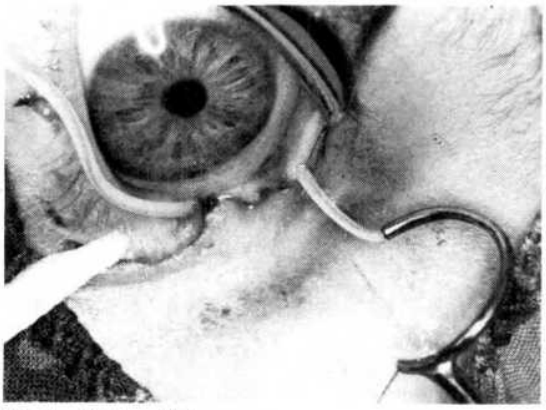

Fig. 7 *Probe withdrawn*

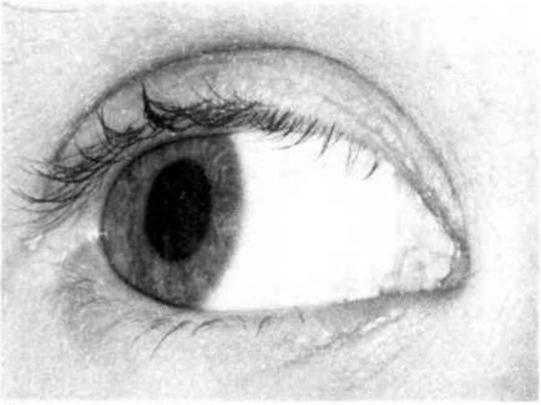

Fig. 8 *Four weeks after original injury*

tissues and the skin, and it has the advantage, particularly in children, in whom this injury is common, of being absorbed. It also produces minimal suture scarring (Fig. 8).

I thank Mr Peter Caudwell, of the Medical Physics Unit at the Royal Hospital, Wolverhampton, for manufacturing the prototype of the instrument and devising the method of fusing silicone tubing to nylon; Mrs Helen Price, of the Department of Medical Photography of the same hospital, for the illustrations; and the staff at the Wolverhampton Eye Infirmary for their helpful advice.

The cannulated probe and silicone tubing are manufactured by Dixey & Co Ltd.

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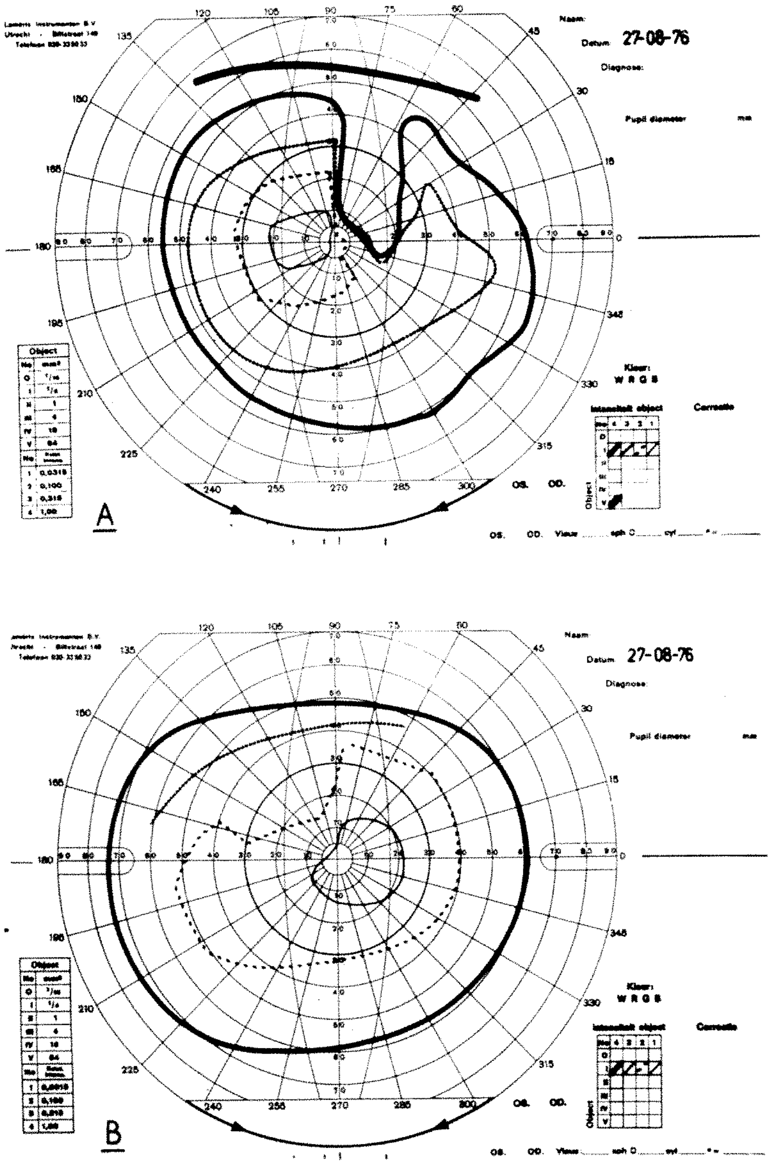

Fig. 2 A, *right eye*; B, *left eye*. *Deterioration of the bitemporal defects in a period of 23 days (27 August 1976)*

which usually disappears after delivery (Carill, 1923; Finley, 1934).

Of special interest is the production or activation of pituitary adenoma during pregnancy (as was the case with our patient). Duke-Elder (1949) states: 'The evidence is strong that in certain cases during pregnancy adenomatous changes may be stimulated or accelerated in the pituitary, that these may eventually involve complete bitemporal hemianopia and may progress in subsequent pregnancies so that eventual operative removal of the neoplasm is necessary'. Definite rules for treatment are difficult to give. Enoksson *et al.* (1961) state that if chiasmal compression is detected during early pregnancy the tumour should be treated according to ordinary neurosurgical principles, that is, removed as soon as possible.

If compression is revealed during the *last* 3 months of pregnancy, expectant treatment under continued surveillance of the visual fields is preferable. Rapid,

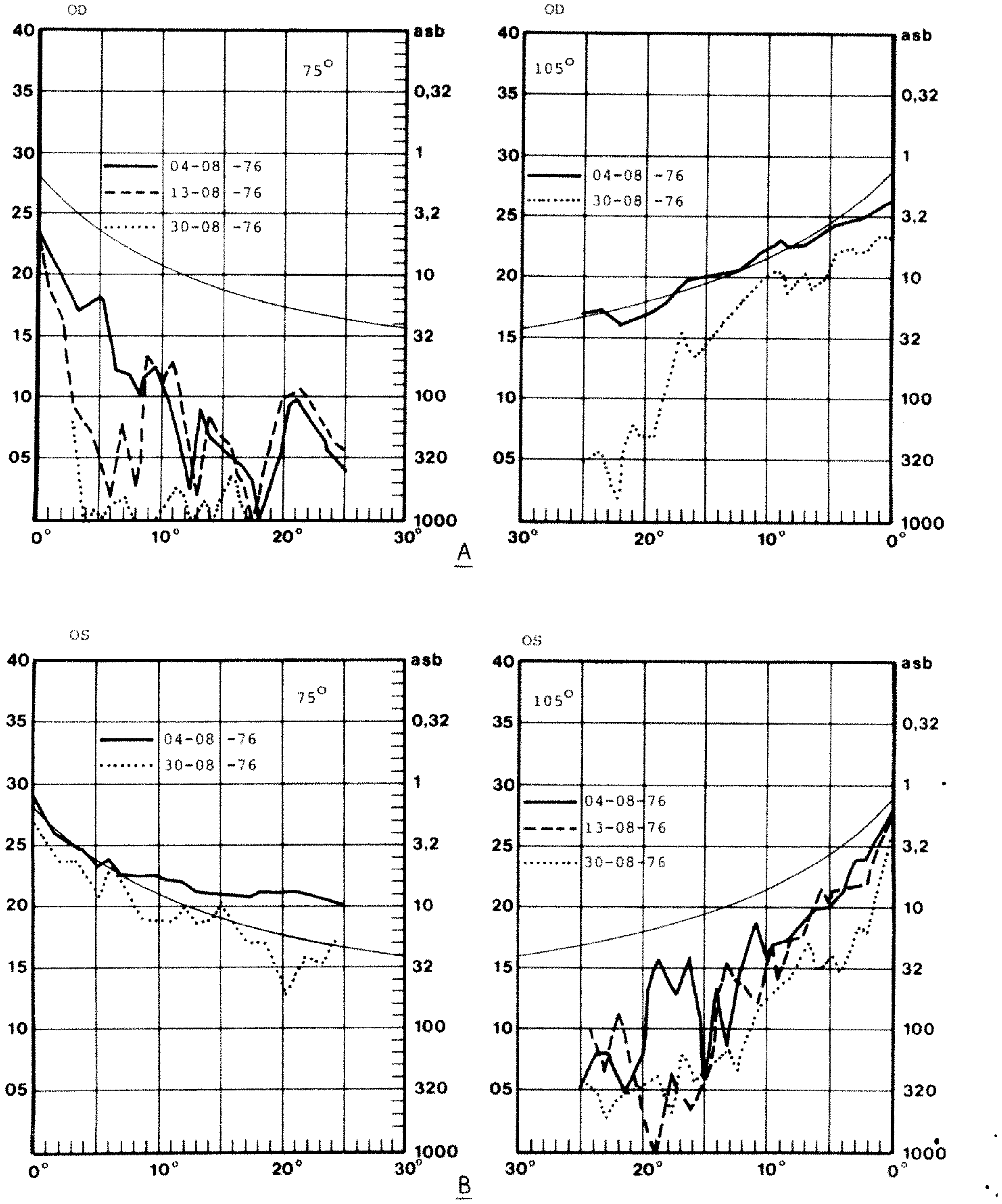

Fig. 3 A, *right eye;* B, *left eye. Follow-up of the bitemporal defects by means of static perimetry*

British Journal of Ophthalmology, 1977, **61**, 729–733

Rapid deterioration of visual fields during bromocriptine-induced pregnancy in a patient with a pituitary adenoma

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SUMMARY A 28-year-old woman with an amenorrhoea–galactorrhoea syndrome was suspected of a microadenoma of the pituitary. She was treated with bromocriptine. In the subsequent pregnancy she developed rapid deterioration of the visual fields (ODS). A large temporal defect in the right eye and a moderate temporal defect in the left eye appeared in the 28th week of pregnancy, threatening the visual acuity of both eyes. Other examinations showed no evident lesion of the sellar region. An adenoma of the pituitary was removed, and the visual fields returned to normal after operation.

Secondary amenorrhoea in combination with galactorrhoea is highly suggestive of the presence of a pituitary or parapituitary lesion. When ovulation is induced by chemical means in such cases, careful attention should be paid to changes in these pituitary or parapituitary lesions.

Patients with amenorrhoea and galactorrhoea were described by Corbey *et al.* (in press), Lamberts *et al.* (in press), and Kajtar and Tomkin (1971). In subsequent (induced) pregnancies visual field defects developed, leading to termination of the pregnancy in the 39th week in one case (Corbey), spontaneous regression of the defects after the 36th week of pregnancy (Lamberts), and performance of hypophysectomy in a third patient (Kajtar and Tomkin). In this third case there was gross erosion of the posterior clinoids, and a pituitary adenoma was found.

Case history

A woman, now aged 25 years, was first seen in our ophthalmology department in July 1975, having been referred to us by the gynaecologist. After a period on oral contraceptives (1970–2) she had developed oligomenorrhoea and galactorrhoea, followed in 1973 by amenorrhoea. In July 1975 high prolactin levels were found (87 ng/ml; normal value 20 ng/ml), and it was concluded that this patient had a prolactin-producing microadenoma of the pituitary gland. Physical examination showed no special features. Tomography of the sellar region showed a slight and equivocal irregularity of the floor of the sella turcica. In March 1976 bromocriptine treatment was started to restore ovarian function. The subsequent pregnancy was normal from the obstetric point of view, and the patient had no complaints. The prolactin level returned to normal (18 ng/ml), and a stereo *x*-ray of the sella turcica showed *no* abnormalities. In the meantime periodic assessments of the visual fields were started.

On 4 August 1976 the first bitemporal defects were found (Fig. 1). On 27 August 1976 a dense temporal defect had developed in the right eye, including a relative central defect. The left eye showed an increase of the temporal defect (Fig. 2). Visual acuity was OD 5/5, OS 5/5. In Fig. 3 the follow-up by means of static perimetry is demonstrated. As a routine procedure we examined the 75° and 105° meridians. In the characteristic early stages the 75° meridian of the right eye is affected and the 105° meridian of the left eye, the 105° (RE) and the 75° (LE) meridians being normal. In a later stage the 105° (RE) and the 75° (LE) meridians also show a defect.

Because of the rapid deterioration of the visual fields the patient was admitted to the Department of Neurology of the Wilhelmina Gasthuis on 31 August 1976. Bilateral carotid angiography, performed on 1 September 1976, gave little or no indication of a pituitary lesion.

Sella tomography was not performed (because of

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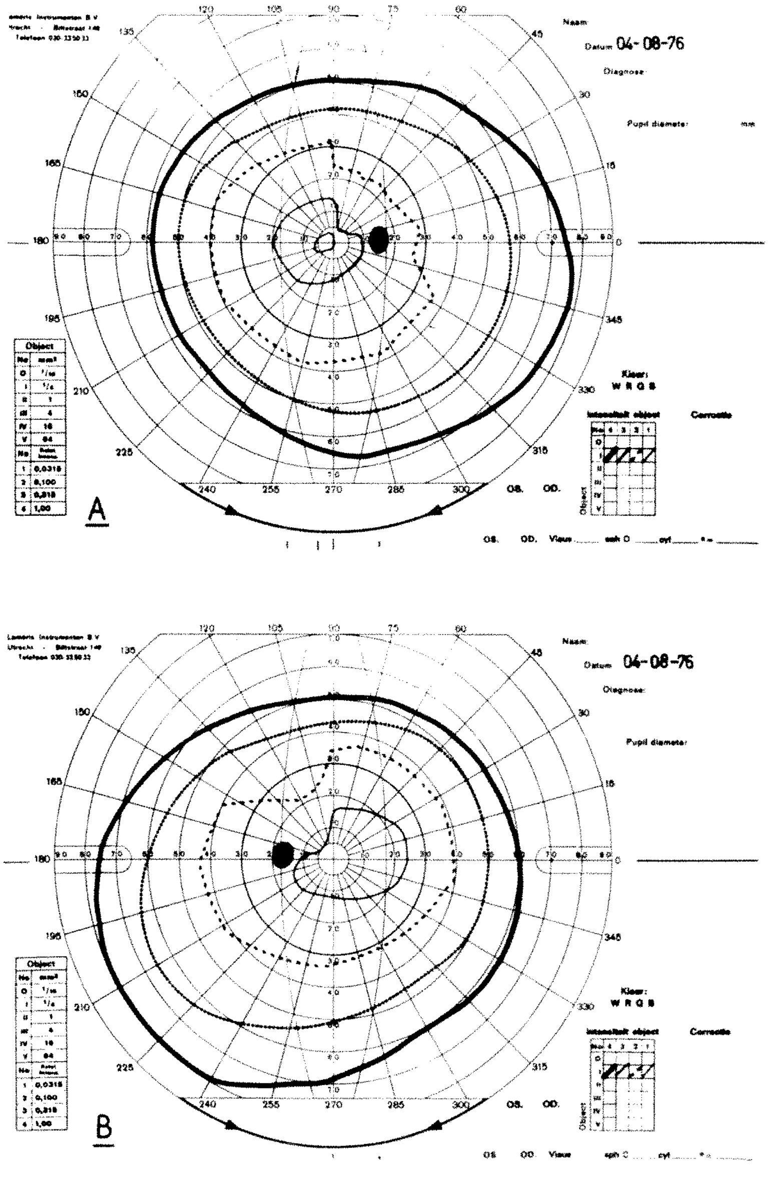

Fig. 1 A, *right eye;* B, *left eye. Early bitemporal defects as shown by the Goldmann perimeter (4 August 1976)*

the risk of radiation exposure). On 5 September 1976 the patient was transferred to the Neurosurgical Department of the Wilhelmina Gasthuis for surgery, and a small adenoma of the pituitary was found. At the time of operation the pregnancy was 28 weeks and obstetrically normal.

Postoperatively the visual fields returned to normal.

Mother and child are in good health at the time of publication of this report.

Discussion

It is well known that the pituitary gland increases in volume during pregnancy. This enlargement is moderate, and it seems unlikely that the increase in volume during pregnancy would cause chiasmal compression, although according to several authors a large percentage of pregnant women develop defects in their visual fields, varying from a peripheral contraction to a bitemporal hemianopia, severe deterioration of vision may then indicate either immediate craniotomy or, if the child is viable, induction of labour.

Hagedoorn's criteria for hypophysectomy were the following (Hagedoorn, 1937): 'In cases with bitemporal hemianopia, if vision in the better eyes diminishes to one-third to one-half, pregnancy should be terminated. If abortion is refused one may wait till vision in the better eye is 1/40. If a living child is not possible at that time treatment by the neurosurgeon is indicated.' Falconer and Stafford-Bell (1975) stated that the treatment of choice whenever vision is seriously threatened at any stage of pregnancy is a surgical attack on the pituitary, followed by suitable replacement therapy to ensure that the pregnancy continues.

In our case the visual fields showed very rapid deterioration, passing in approximately 30 days from almost normal to a large bitemporal defect in one eye and a moderate defect in the other eye, threatening the visual acuity of both eyes, and strongly suggesting the presence of an active pituitary adenoma (at that time the pregnancy was 28 weeks).

There were no really convincing radiographic changes in the sellar region, so that the patient was subjected to operation on the grounds of the increase in the visual field defect as detected by means of the careful and repeated perimetry, including static perimetry. Moreover, our patient was rather a rarity in that she had evidence of a pituitary (micro) adenoma and a pregnancy 'induced' with bromocriptine.

The visual fields returned to normal after decompression, showing that the operation was performed in time. The reversibility of bitemporal defects in the visual fields after surgical decompression of the chiasma depends on the extent and intensity of the compression. Long-standing absolute defects usually show little postoperative regression. The performance of hypophysectomy in this patient averted the need for a (premature) termination of the pregnancy.

Conclusions

A pregnant woman suspected of a pituitary lesion should have frequent and careful perimetric examinations. This report of bitemporal defects in the visual fields in a bromocriptine-induced pregnancy following an amenorrhoea–galactorrhoea syndrome seems to indicate that surgical decompression of the chiasma can be considered in such cases.

We thank Miss M. A. Raakman for the skilful perimetry.

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Book reviews

Modern Problems in Ophthalmology. Vol. 18. Turning Points in Retinal Surgery. Edited by E. B. STREIFF, E. W. D. NORTON, C. GAILLOSEL, and B. DAICKER. 1977. Pp. 546, figs, refs. Karger, Basle (DM245)

This book reports the tenth meeting of the Jules Gonin Club. The five main topics dealt with are ultrasonography and retinal detachment, the diagnosis and treatment of retinoblastoma, vitreous surgery, recent advances in chorioretinal surgery, and the influence of changing cataract technique on retinal pathology and surgery.

As is usual in the Gonin Club, the topics dealt with are assessed by international retinal experts and offer an interesting cross-section of techniques currently employed. Now that vitreous surgery is being widely practised, the ultrasonography sections underline the value and necessity of this investigation, which provides the surgeon with information about the retina in the presence of opaque media. A large series of retinoblastomas treated in London is reported, reflecting steady improvement in technique and prognosis.

The relatively new subject of vitreous surgery is comprehensively discussed. This topic has attracted a large number of different instruments for performing this operation, and there are papers from protagonists of the different machines. Of particular significance has been the contribution from the Miami Retinal Group. In the same section the use of intraocular gases is dealt with. Recent advances in choroidoretinal surgery demonstrate the ingenuity of some authors even though some of the suggestions seem clinically unattractive. The last section deals with the relationship of the anterior segment surgeon to the retinal surgeon, a subject that will be of increasing interest with progressive use of vitrectomy instruments for anterior segment work.

Of particular value in the book are the discussions which highlight the apparent differences between the European and the Anglo-American approach to retinal problems. A minority of papers are published in French and German with English summaries. The book is well produced and makes a fine addition to any library, although it is too specialised for the general ophthalmologist. It is strongly recommended to the retinal surgeon and will provide hours of enjoyable reading.

A. G. CHIGNELL

Becker-Shaffer's Diagnosis and Therapy of the Glaucomas. 4th edn. A. E. KOLKER and J. HETHERINGTON. 1976. Pp. 526, 448 figs., tables, refs. Mosby: St. Louis (£30·50)

A new edition of this excellent text is most welcome, and the authors have managed to improve considerably on the highly regarded previous edition. The book is 31 pages longer and includes fresh work on electron microscopy, outflow studies, visual fields, optic disc changes, and surgical procedures. After an exhaustive classification is an improved chapter on gonioscopy, with many practical hints on technique demonstrated with great clarity. Next come sections beautifully illustrated on gonioscopic and microscopic anatomy and the clinical significance of gonioscopic findings. Tonometry and tonography are dealt with in four sections, the last of which is again an account of clinical applications. Ophthalmoscopy and perimetry are described in the next section, and there follows a section devoted to the principal clinical features of the major classical types of glaucoma. Medical and surgical treatment are then described, the section on surgical operations being comprehensive and clearly illustrated. Of the final chapters the penultimate, in which a series of tonograms are presented, is possibly now of questionable value, but in view of the origins of the book from a stronghold of tonography they have a certain nostalgic quality. And—who knows?—the story of tonometry may not yet be over.

This is a superbly produced textbook which is an adornment to any ophthalmologist's library, and the authors are to be congratulated once again.

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Third Visual Field Symposium

The International Perimetric Society (IPS) will hold the Third International Visual Field Symposium in Tokyo, Japan, on 3–6 May 1978. It is open to all IPS members and their guests. For details contact Dr E. L. Greve, Eye Clinic, University of Amsterdam, Wilhelmina Gasthuis, Eerste Helmerstraat 104, Amsterdam 1013, The Netherlands.

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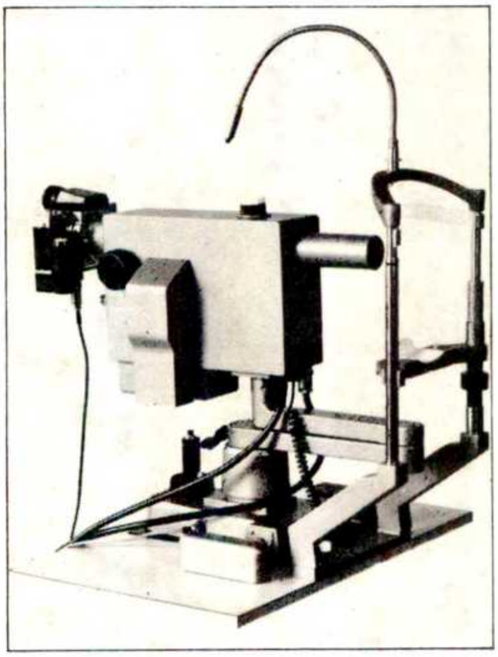

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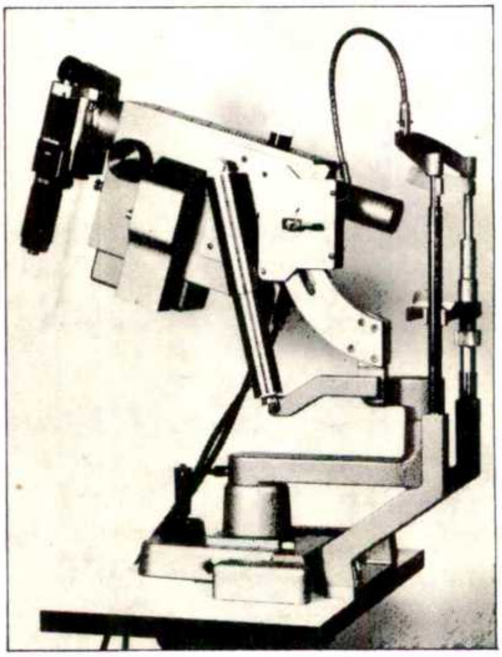

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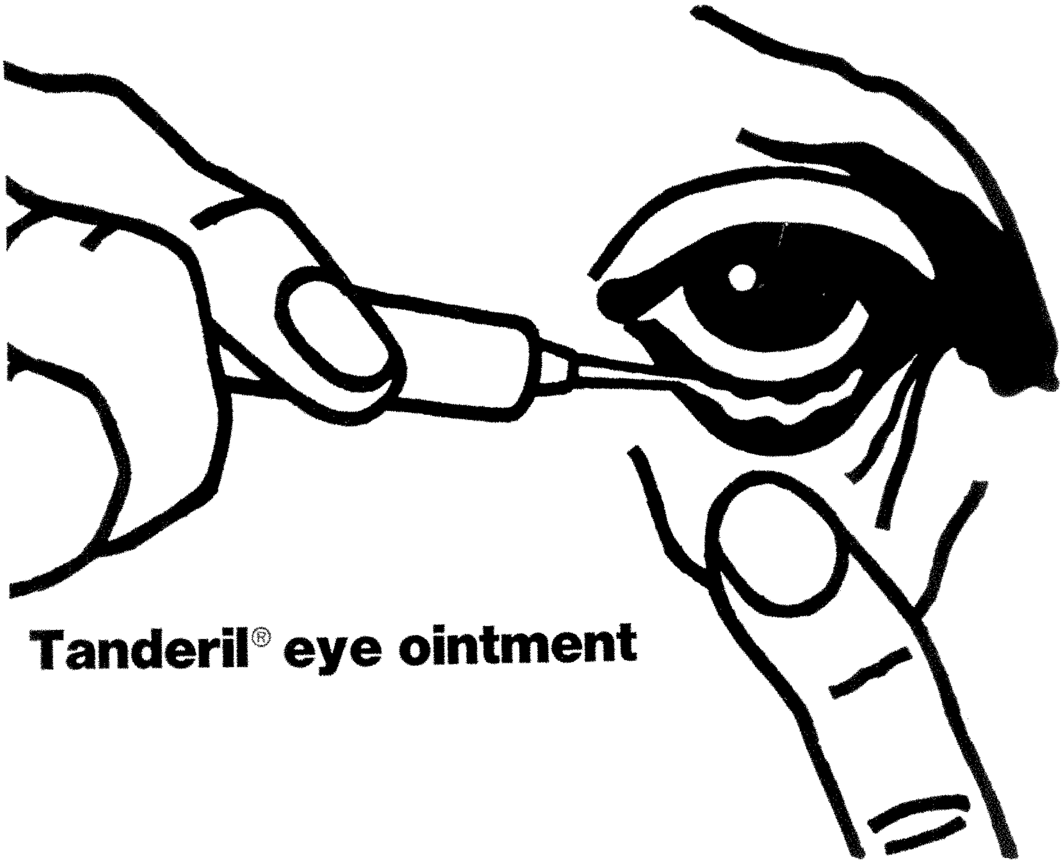

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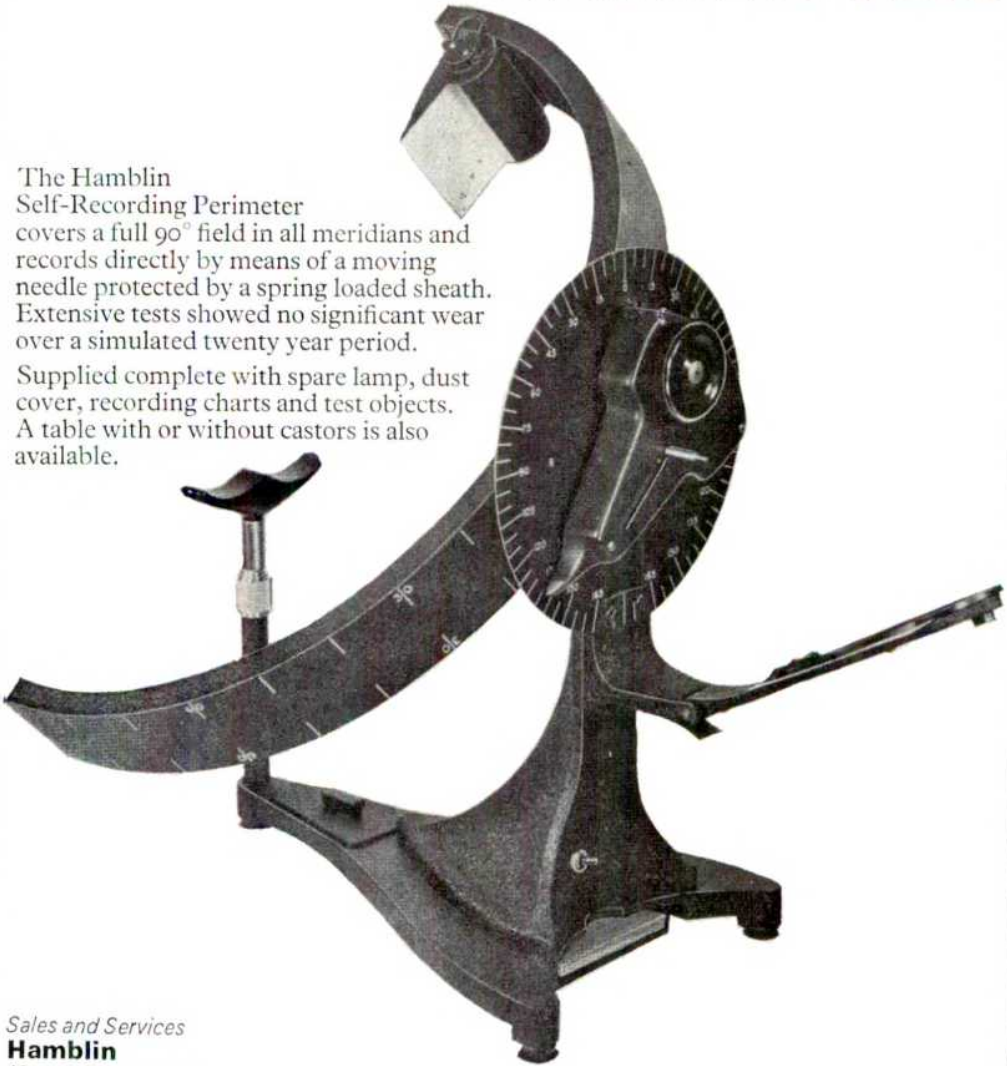

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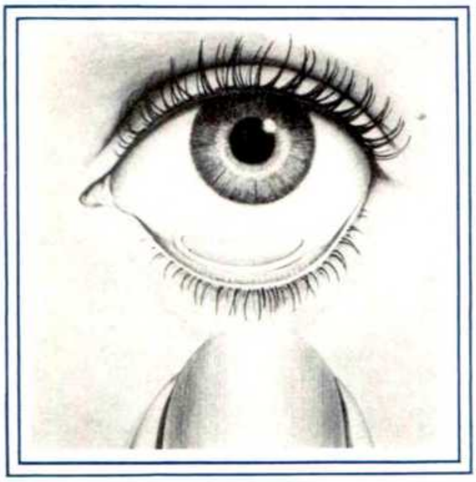

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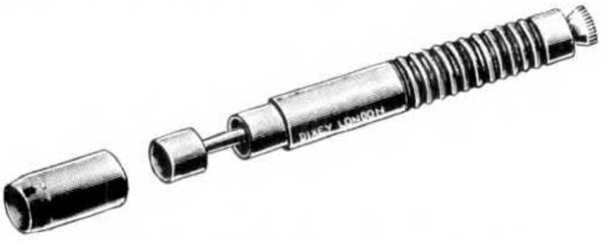

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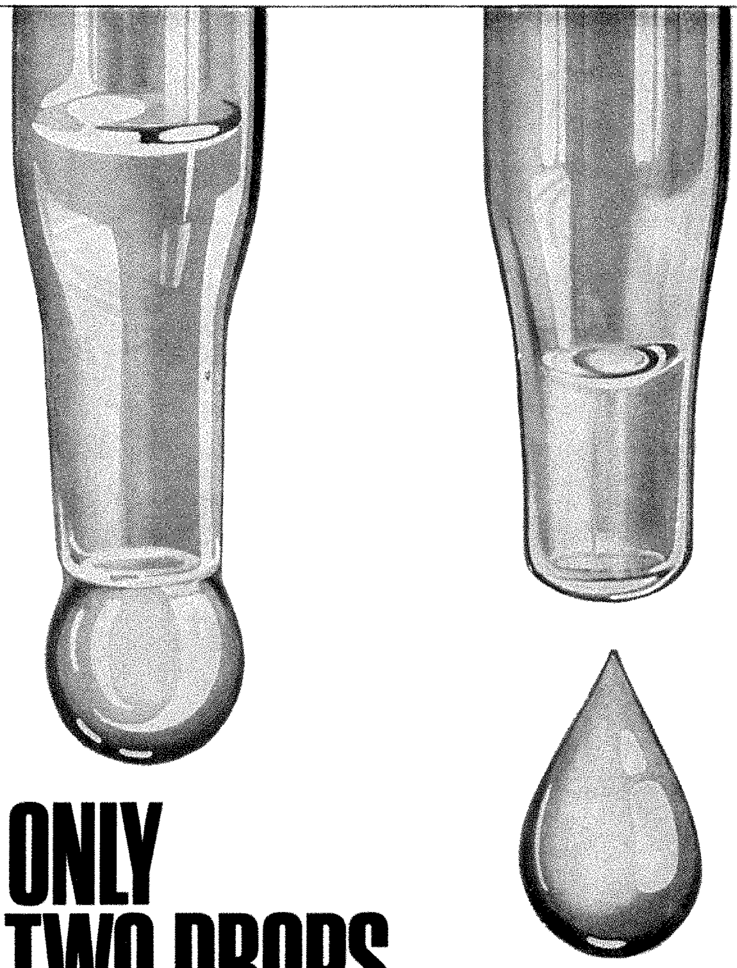

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C-scan ultrasonography in orbital diagnosis

MARIE RESTORI AND JOHN E. WRIGHT
From Moorfields Eye Hospital, London

SUMMARY A C-scan imaging facility has recently been added to the ultrasonic system in use at Moorfields Eye Hospital, London. The technique is explained and typical C-scans are presented to demonstrate the normal orbital fat and optic nerve, together with selected pathological conditions in the orbit. The C-scan facility permits imaging of the orbital contents in the coronal plane. This coronal plane imaging, together with high resolution and sensitivity, makes this a useful technique for demonstrating orbital lesions and it is hoped helps in the accurate measurement of the diameters of the optic nerve along its length. The problems associated with C-scanning are discussed.

The coronal plane of the orbital contents is inaccessible to ultrasonic B-scan investigation because the surrounding orbital walls prove a barrier to the sound beam. This plane may, however, be imaged using a C-scan technique. The C-scan also provides a means of measuring the diameter of the optic nerve, for which purpose it is potentially more accurate than both A-scan and B-scan.

This paper presents preliminary results of clinical trials of a C-scan facility which has recently been added to the Moorfields ultrasonic system (Aldridge *et al.*, 1974). This system is also capable of A-scan, mechanical B-scan (McLeod *et al.*, 1977), and holographic imaging (Restori, 1977).

Methods

The coronal C-scan plane of the orbit, together with the horizontal and saggital B-scan planes, are illustrated in Fig. 1. The method of scanning to obtain a C-scan is illustrated in Fig. 2.

The eye is anaesthetised with oxybuprocaine HCl drops and the eyelids are retracted with a Barraquer speculum. A focused 10 MHz transducer (focal length 46 mm and focal spot diameter 0·8 mm), is coupled to the eye by means of a bath (Purnell, 1966) containing saline at 36°C. A fixation light is used to reduce eye movements to a minimum. To complete the C-scan the transducer sweeps mechanically in a rectilinear fashion to cover a 4 cm square aperture in which the eye is centralised. Each 4 cm sweep of the transducer takes approximately 140 ms to complete. Either 80 or 160 transducer sweeps may be employed to produce a C-scan taking 11 or 23 s respectively to complete. C-scans compiled in 23 s contain more information than those compiled in 11 s and were the option chosen for all C-scans described in this paper. The transducer emits pulses of sound and, in the time interval between emission of pulses, returning echoes are received by the same transducer. Only echoes from within two pre-selected depths within the orbit are recorded, these depths being selected by earlier reference to the B-scan display (Fig. 3). The focal plane of the transducer is arranged to lie at the centre of these chosen depths. The resolution attainable, therefore, is dependent on the focal spot diameter of the transducer (0·8 mm for all C-scans described in this paper). The echoes from the preselected depths correspond to those received within a period of time (time-gate) a certain time after the emission of a pulse from the transducer. If the time-gate is kept narrow, that is the preselected depths are close together, a thin section of tissue may be imaged. The time-gate is normally set at 2 μs which, assuming a short examining pulse of sound, is equivalent to 1·45 mm in thickness of orbital fat. The intensities of the recorded echoes are used to modulate the brightness of the spot of a cathode ray tube, which is driven in synchronism with the transducer. The C-scan images the soft tissues within the time-gate in the coronal plane and is recorded on Polaroid positive/negative film.

Results

To date 82 orbits have been examined using the C-scan in conjunction with the B-scan technique. C-scan examination was employed in all cases of suspected optic nerve lesions or for those lesions

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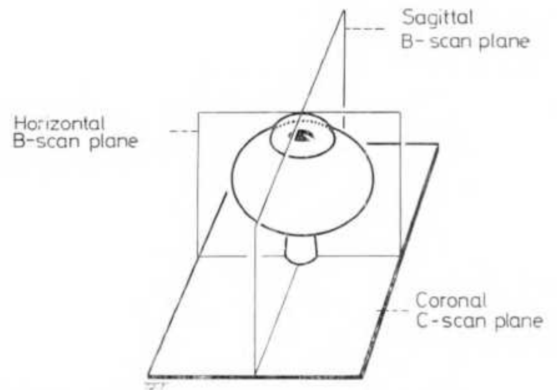

Fig. 1 *Planes of B-scan and C-scan examinations*

in which it was important to ascertain their position relative to the optic nerve. In addition, C-scan investigations were performed whenever there was some doubt about the nature or extent of an orbital lesion.

A normal C-scan section taken a few millimeters behind the globe is shown in Fig. 4. Individual lobules of fat can be delineated and the optic nerve is seen as an acoustically clear area. A variety of pathological changes in the orbit are demonstrated in Figs 5 to 8.

The C-scan in Fig. 5 displays a meningioma surrounding the optic nerve. The echoes arising from this mass represent sound scattered by the tumour, possibly by psammoma bodies which were demonstrated histologically. These echoes were not demonstrated on the B-scan display. A lymphoma wrapped around the optic nerve is illustrated in the C-scan (Fig. 6). The optic nerve lies within

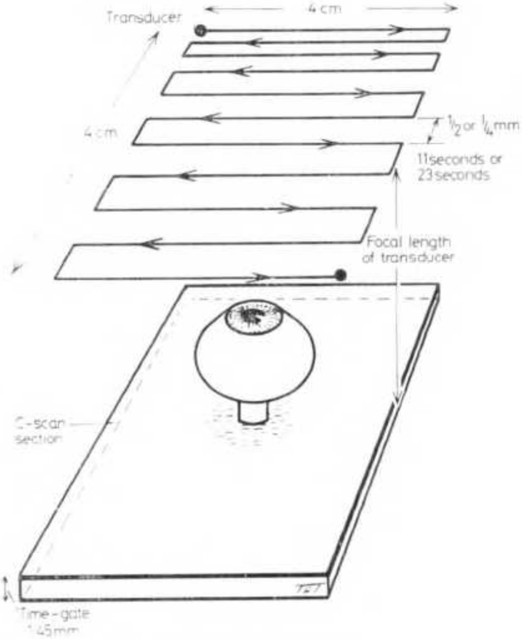

Fig. 2 *C-scan imaging of the orbit*

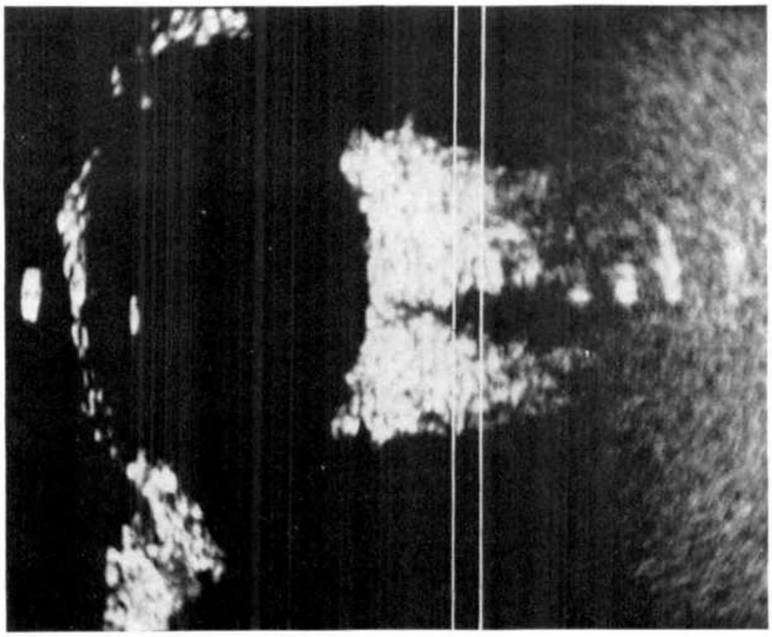

Fig. 3 *B-scan section showing preselected depths (time-gate) in a normal orbit for C-scan examination*

the clear area in the centre of the fat pad, and is surrounded by the acoustically homogenous lymphoma. As neither the mass nor the optic nerve gives rise to echoes the exact border of the nerve can only be surmised. The mass is seen to be lobulated. The attenuating properties of this mass, its homogenous nature, and the lobulated shape which was well demonstrated on C-scanning, led to a correct preoperative ultrasonic diagnosis of lymphoma.

The distorted fat pad of a dysthyroid patient is shown in Fig. 7. The grossly enlarged superior rectus muscle is seen as an acoustically clear area above the optic nerve. The full extent of the enlarge-

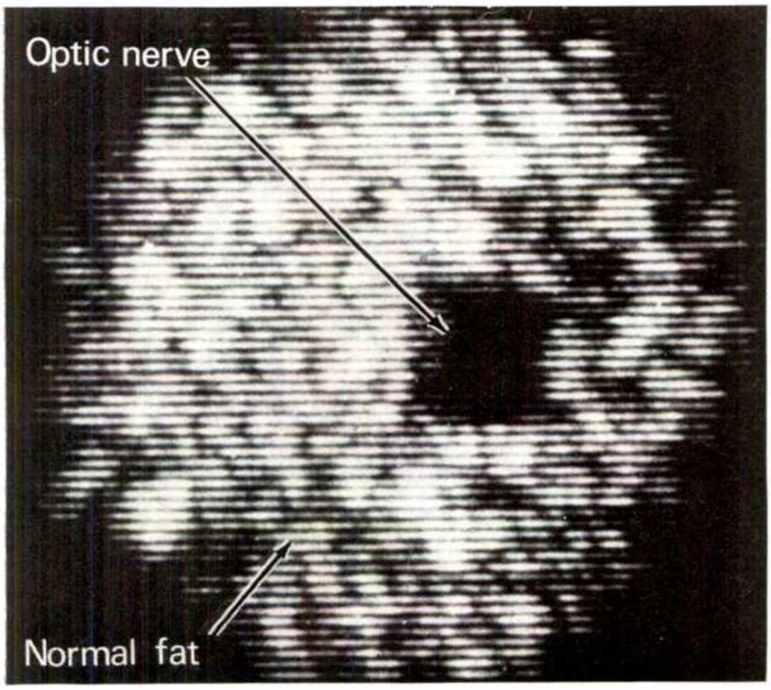

Fig. 4 *A normal fat pad in C-scan section*

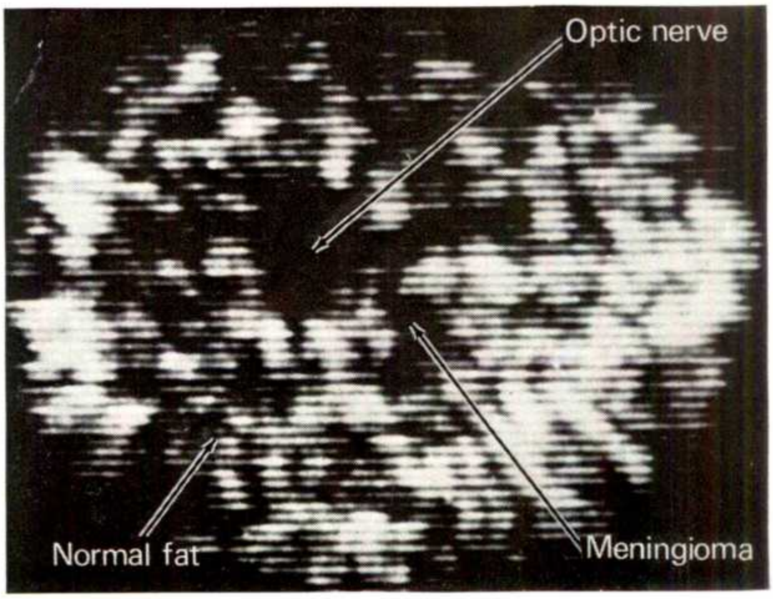

Fig. 5 *Optic nerve meningioma in C-scan section*

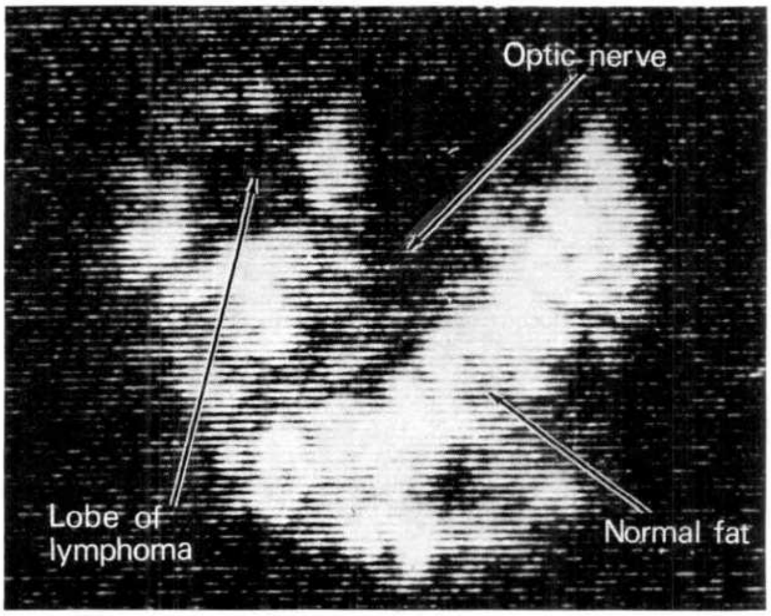

Fig. 6 *C-scan section showing lobulated lymphoma around the optic nerve*

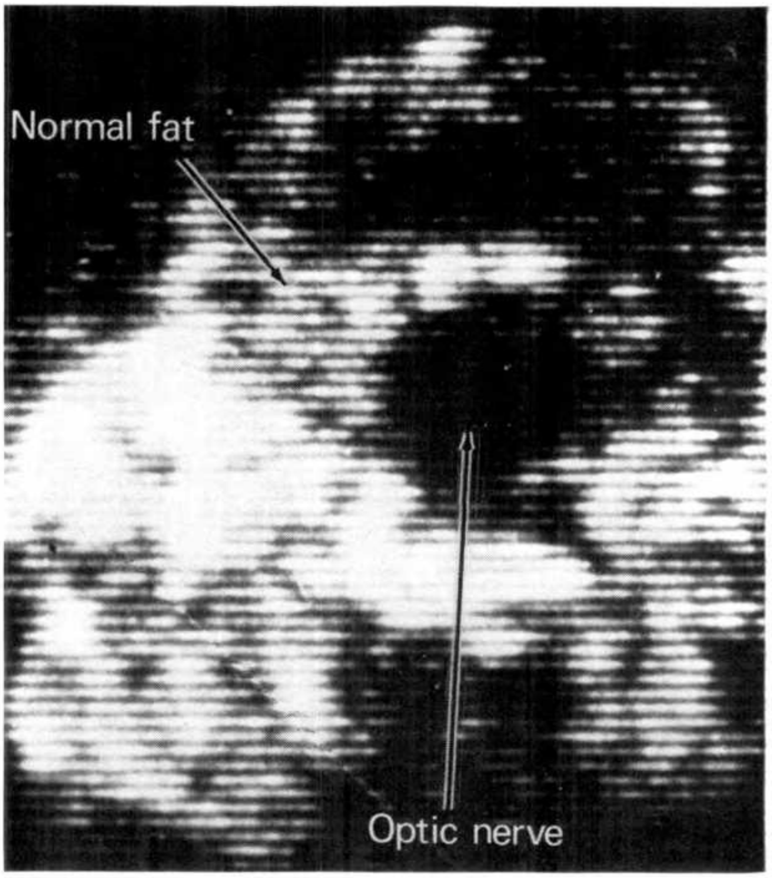

Fig. 7 *Fat pad of dysthyroid patient with enlarged superior rectus muscle seen directly above the optic nerve—C-scan*

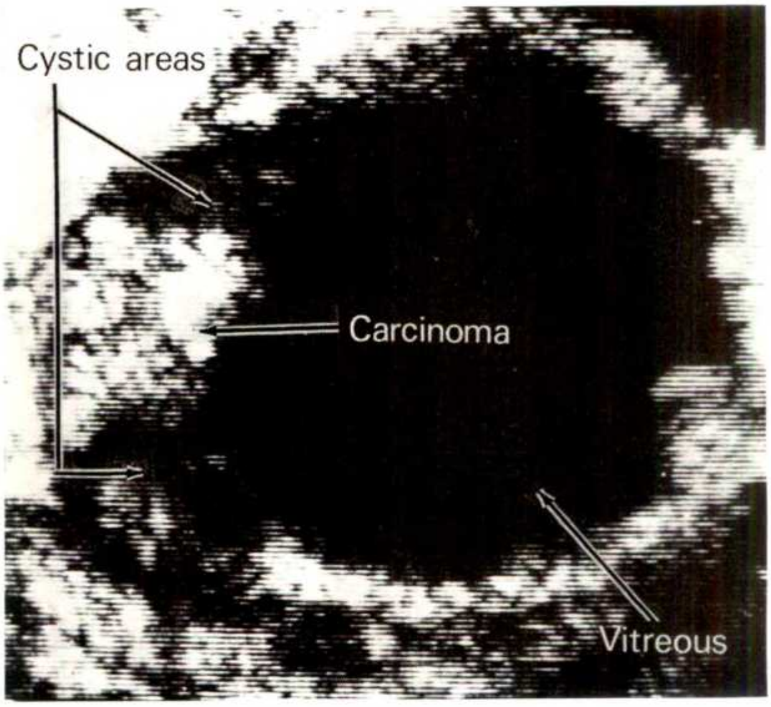

Fig. 8 *Mass originating in the lacrimal gland shown in coronal C-scan plane*

ment was determined by means of consecutive C-scan sectioning of the orbit. In Fig. 8 a large lacrimal mass is illustrated and its position in relation to the globe is demonstrated. The indentation of the superotemporal equator of the globe by the mass is clearly illustrated. Part of the mass gives rise to echoes, while other parts of the mass appear acoustically homogenous. This mass proved at surgery to be a lacrimal carcinoma lying within a cyst.

Discussion

Several authors (McCready and Hill, 1971; Northeved *et al.*, 1974; Suarez *et al.*, 1975) have discussed the possibility of employing a C-scan modality in medical diagnosis, but the technique has not been widely used. C-scanning of the orbit has proved to be particularly useful as it displays that plane in the fat pad which the surgeon progressively dissects during lateral orbitotomy. In addition, the position of lesions in relation to the optic nerve can be clearly demonstrated. The C-scan technique used in conjunction with the B-scan also permits three mutually perpendicular planes within the orbit to be visualised, such that the full extent and shape of a lesion can often be determined.

In the C-scan technique, the focal plane of the transducer is arranged to coincide with the plane to be imaged so that certain advantages accrue. Firstly the power of the sound beam is at a maximum in the focal region, and thus the transducer is at its most sensitive here. This high sensitivity allows low amplitude echoes to be detected and, therefore, more information about the likely nature of a mass is received. Secondly, the sound beam is narrowest in the focal region, and equal to the focal spot diameter of the transducer. Consequently, since the resolution on the C-scan depends on the width of the examining sound beam in the imaged plane, resolution is optimised.

C-scan imaging employing strongly focused transducers, and hence having very small focal spot diameters, could be used as a means of measuring the diameter of the optic nerve with high resolution. It is intended to employ such transducers in a future study, correlating results with measurements taken at surgery. The C-scan has advantages over both B-scan and A-scan techniques for these measurements. The B-scan is limited by the width of the examining sound beam, and as transducers suitable for B-scan are only weakly focused, the resolution attainable is not as great as that possible employing a C-scan technique. The A-scan measurements are limited by the difficulty in arranging the sound beam to strike the optic nerve perpendicularly, a prerequisite for accurate A-scan measurement. Thus the diameter of the optic nerve tends to be overestimated.

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C-scans are degraded by gross eye movements or by small involuntary movements (Coleman, 1971) occurring during construction of the image; for this reason attempts are made to keep such movements to a minimum. C-scans taking 11 s rather than 23 s to complete may be the option chosen for patients who find difficulty in holding the eye still. Because the orbital fat is more static than the eye, it is less susceptible to such degradation and thus lends itself to C-scan examination.

The authors would like to thank Terry Tarrant for all illustrations and Erica Banks for her secretarial assistance.

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Panretinal photocoagulation in central retinal vein occlusion: a randomised controlled clinical study

L. LAATIKAINEN, E. M. KOHNER, D. KHOURY, AND R. K. BLACH
From the Retinal Diagnostic Unit, Moorfields Eye Hospital, London

SUMMARY A randomised controlled study of photocoagulation compared with no treatment in central retinal vein occlusion is reported. Forty-eight patients were allocated into treated and control groups by a random procedure 3 months after their first visual symptoms. For the analysis they were subdivided into (1) ischaemic type, and (2) hyperpermeability-response macular-oedema type of central retinal vein occlusion.

In neither group did treatment confer benefit as far as visual acuity was concerned. However, iris, disc, and retinal neovascularisation improved after treatment in the ischaemic group. In addition none of the treated patients progressed to neovascular glaucoma. Macular-oedema improved in treated patients with the hyperpermeability response, but the visual field was affected and atrophic changes at the macula precluded visual improvement.

It is concluded that photocoagulation should be used only to prevent complications in the ischaemic type of central retinal vein occlusion. It does not appear to be of value in the hyperpermeability group.

Photocoagulation has been shown to be effective in the treatment of both macular oedema and neovascularisation in diabetic retinopathy. It is therefore reasonable to assume that similar results can be achieved in retinal vein occlusion, where macular oedema and new vessel formation are common complications. There are several reports indicating 'good results' (Zweng *et al.*, 1974; Theodossiadis *et al.*, 1974; Freyler and Nichorlis, 1974; Wetzig and Thatcher, 1974; Oosterhuis and Sedney, 1975; Sedney, 1976), but none of these was a randomised controlled clinical study. In order to determine the exact place of photocoagulation in the treatment of central retinal vein occlusion (CRVO) a randomised controlled trial was carried out at Moorfields Eye Hospital during 1975–7. The results of this study are presented in this communication.

Patients and methods

PATIENTS

All patients with recent CRVO (less than 3 months' duration of symptoms) referred to the Retinal Diagnostic Unit at Moorfields Eye Hospital in 1975 were considered for the trial. The patients were assessed and followed up without treatment until 3 months after initial visual symptoms. At the 3-month examination patients whose visual acuity was 6/24 or worse entered the study provided they did not have neovascular glaucoma or other eye disease affecting vision and precluding treatment, and provided they agreed to randomisation.

Randomisation was by the use of pre-prepared sealed envelopes which indicated whether an eye was for treatment by photocoagulation or remained untreated, i.e., control. No other therapy for vein occlusion was given to any of the patients, but glaucoma and medical conditions were treated as required. There were 24 treated and 24 control patients. The mean age of the patients was 62 years (range 44–79 years) in the treated and 61·6 years (range 36–79 years) in the untreated group.

The patients were followed up for at least 1 year after entering the trial whenever possible. Five patients were not followed up for the required time. Two died, 4 and 10 months after entering the trial, 1 left the country, and 2 defaulted from follow-up.

During the course of the study the initial scheme was slightly modified so that eyes with considerable capillary closure were entered into the trial as soon as the first fluorescein angiogram became available, i.e., before 3 months expired.

Prior to analysis patients were subdivided into two subgroups according to the main cause of visual loss as revealed by fluorescein angiography. The

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groups were: (1) Ischaemic group with predominant retinal capillary closure (12 treated and 11 control patients). (2) Predominant macular oedema characterised by only small areas of capillary non-perfusion at the posterior pole and dilated capillaries with marked leakage (hyperpermeability response). There were 12 treated and 13 control patients.

METHODS

All patients had a full medical and ophthalmological examination, including visual acuity, slit-lamp examination of the anterior segment, applanation tonometry, gonioscopy, Goldmann perimetry, direct and indirect ophthalmoscopy, fundus photography, and fluorescein angiography. In most cases iris angiography was also performed. Follow-up examination was at 3 months, 1 month after entering the trial and 3 monthly thereafter until 1 year, whenever possible. At every visit visual acuity and intraocular pressure as well as changes in the iris and fundus were recorded, and photography was repeated. The visual field was checked once after treatment.

For treatment the O'Malley Log II xenon arc photocoagulator was used. After retrobulbar anaesthesia of 1·5 ml 2% lignocaine hydrochloride approximately 400 burns (range 250–550) of 4·5° spot size were applied as a 360° panretinal photocoagulation, leaving the macular area inside the temporal vascular arcade untreated. All patients were treated as outpatients in one or two sessions. In 7 patients the treatment was completed by argon laser burns (Coherent Radiation Model 800 laser).

Results

VISUAL ACUITY

The visual acuity results are shown in Figs. 1 and 2. Visual outcome in the ischaemic group was poor (Fig. 1*a*, *b*). Among the treated patients 2 improved by 2 lines on the Snellen chart, 4 remained unchanged, 5 deteriorated, 1 to no perception of light. In the control group 1 of 11 improved by 4 lines, one by 2 lines, 5 remained unchanged, and 4 deteriorated, 1 to no perception of light. The one untreated patient who improved re-established drainage of the inferior temporal quadrant with improvement of the perifoveal capillary circulation.

Visual outcome in the macular oedema group was also poor. In all treated and untreated eyes remained within one line of the initial visual acuity (Fig. 2*a*, *b*). The difference between the treated and untreated eyes was not significant.

VISUAL FIELDS

In the ischaemic group with extensive capillary closure marked constriction of the visual field was

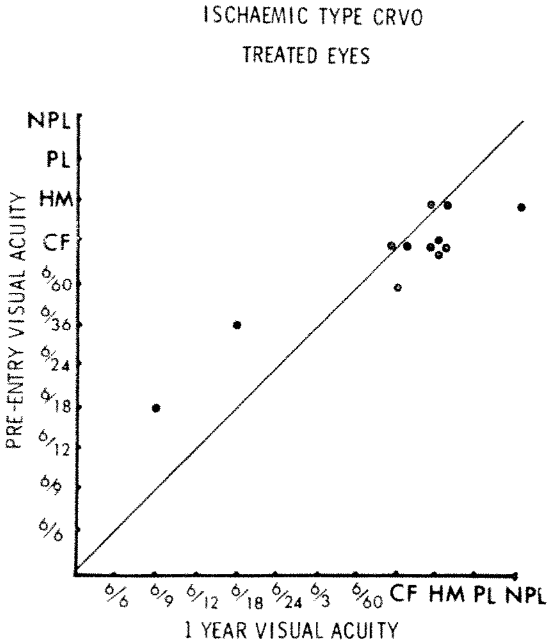


Fig. 1*a* *Pretreatment versus 1 year visual acuity in patients with predominant capillary closure who had treatment by photocoagulation*

CF = *counting fingers. HM* = *hand movements.*
PL = *perception of light. NPL* = *no perception of light*

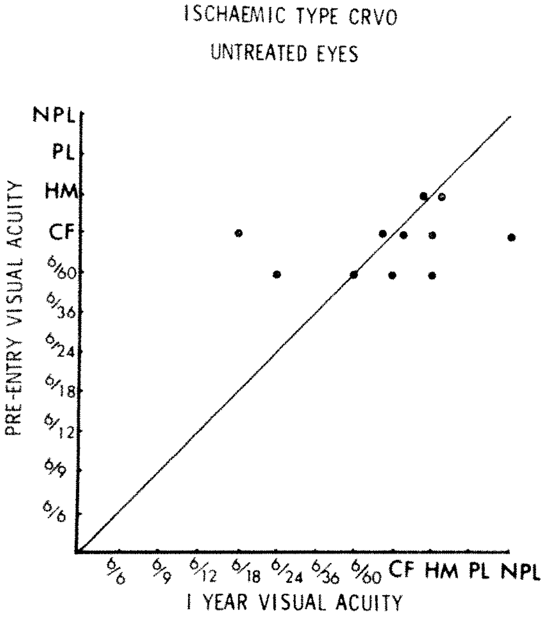


Fig. 1*b* *Pre-entry versus 1 year visual acuity in patients with predominant capillary closure who had no treatment*

common finding (Fig. 3) (although in a few cases normal peripheral isopter was found using a large bright test object (Fig. 4*a*)). No improvement of the visual fields was found in any of the cases if the macula was affected. In most instances the visual field deteriorated owing to complications described later or to post-treatment retinal scarring (Fig. 4*b*).

In the macular oedema group relative scotomas of various sizes were found in all cases studied (Fig. 5*a*, 6*a*). In some eyes enlargement of the blind spot and/or constriction of the peripheral field as com-

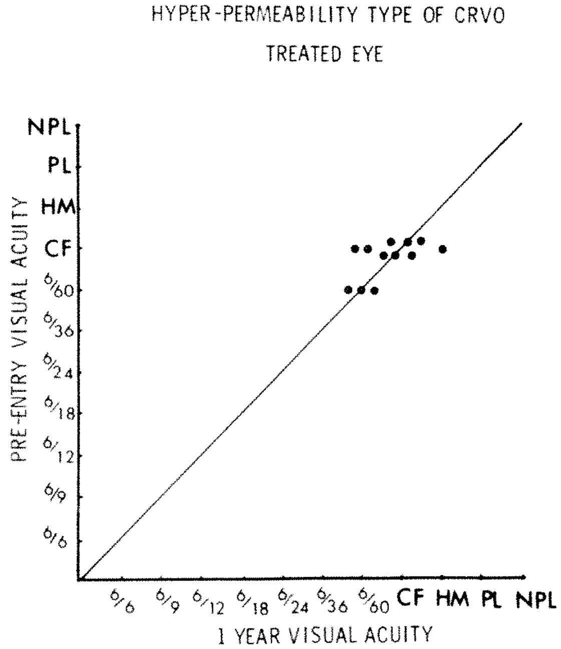


Fig. 2*a* *Pretreatment versus 1 year visual acuity in patients with the hyperpermeability, macular-oedema response, who had treatment by photocoagulation*

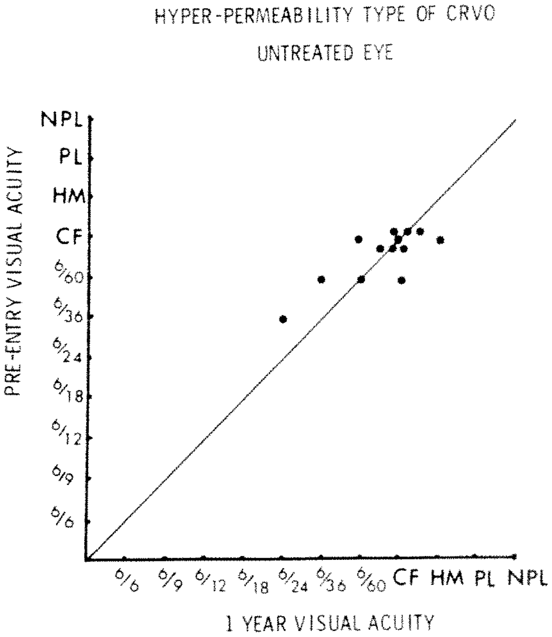


Fig. 2*b* *Pre-entry versus 1 year visual acuity in patients with the hyperpermeability response who had no treatment*

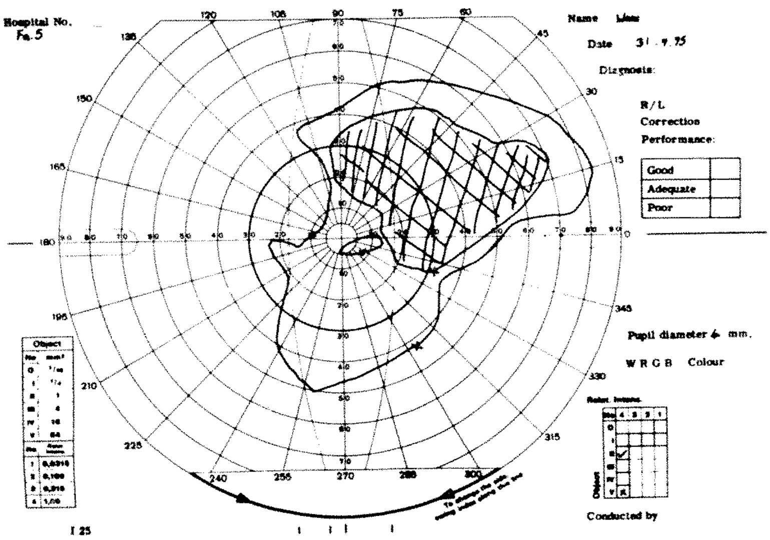


Fig. 3 *Visual field in ischaemic type of CRVO showing marked constriction without treatment*

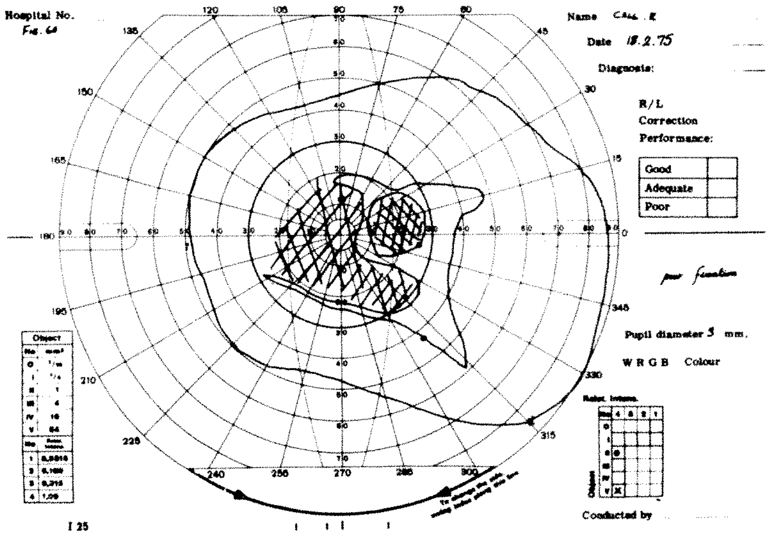


Fig. 4*a* *Visual field in ischaemic type of CRVO before photocoagulation with central scotoma but preservation of the peripheral field*

pared with the other eye was also found (Fig. 5*a*). During the follow-up the central scotoma became smaller in both the untreated (Fig. 5*b*) and the treated cases, but in the treated eyes considerable constriction of the peripheral field was seen (Fig. 6*b*).

IRIS NEOVASCULARISATION AND NEOVASCULAR GLAUCOMA

The diagnosis of rubeosis iridis was based on clinically visible neovascularisation. Iris neovascularisation was not seen in any of the eyes with a hyperpermeability-response, macular-oedema group. However, it did occur after 27 months after the initial symptoms in 1 patient in this group, who at that time developed widespread capillary closure in the retinal periphery. Iris changes in the ischaemic group are summarised in Table 1.

In the treated group 5 out of 12 eyes with the ischaemic type of occlusion already had some rubeosis at entry into the trial. In 4 of these eyes rubeosis disappeared after photocoagulation and in 1 eye it decreased considerably (Fig. 7*a*, *b*, *c*). In contrast, in 2 eyes mild peripupillary neovascularisation appeared after treatment. None of the

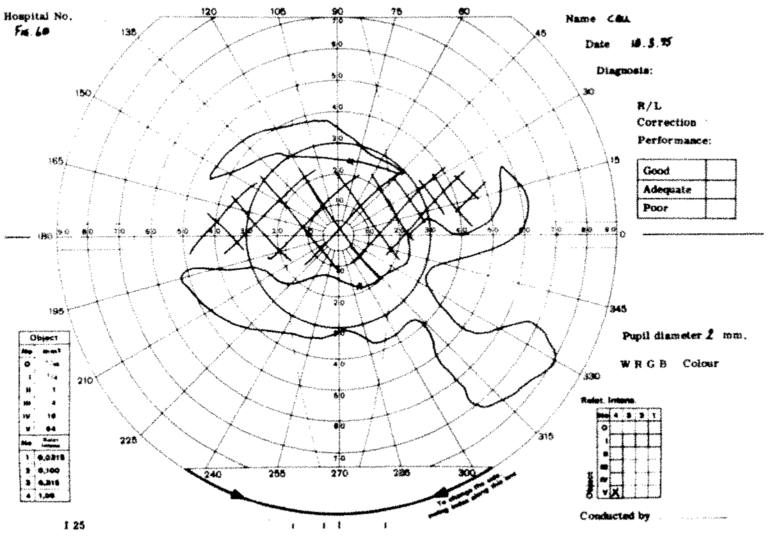


Fig. 4*b* *Same as Fig. 4*a* *but after panretinal photocoagulation*

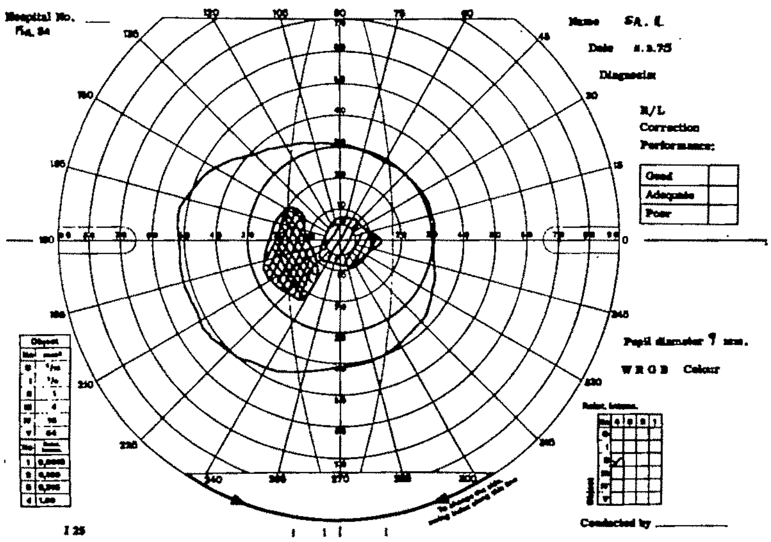


Fig. 5a *Visual field in macular oedema type of CRVO showing central scotoma and enlargement of blind spot*

treated eyes have developed neovascular glaucoma.

In the untreated group 1 out of 11 eyes with the ischaemic type of occlusion had mild rubeosis at entry into trial. During the follow-up iris neovascularisation in this eye increased considerably centrally around the pupil, but the angle remained open and the intraocular pressure normal (Fig. 8*a*, *b*, *c*, *d*). In 5 eyes iris neovascularisation developed during the follow-up period, and 2 of these progressed to neovascular glaucoma. One of the 3 eyes with normal intraocular pressure in spite of rubeosis developed extensive retinitis proliferans as well (Fig. 9*a*, *b*).

Table 1 *The occurrence of iris neovascularisation and neovascular glaucoma in the ischaemic type of CRVO*

	Treated group	*Untreated group*
Number of cases	*12*	*11*
Rubeosis present at the onset of trial	5	1
Rubeosis decreased or disappeared during the follow-up	5	—
Rubeosis developed during the follow-up	2	5
Neovascular glaucoma developed	—	2

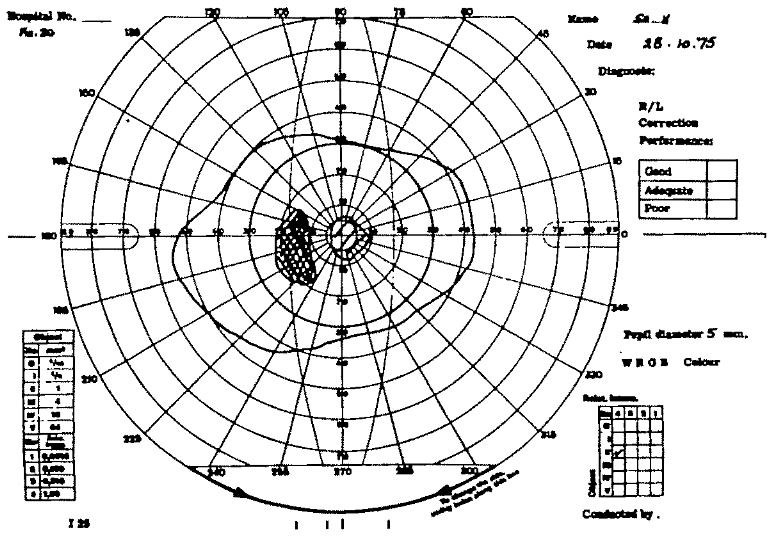


Fig. 5b *Same as Fig.* 5a *but 7 months later without treatment*

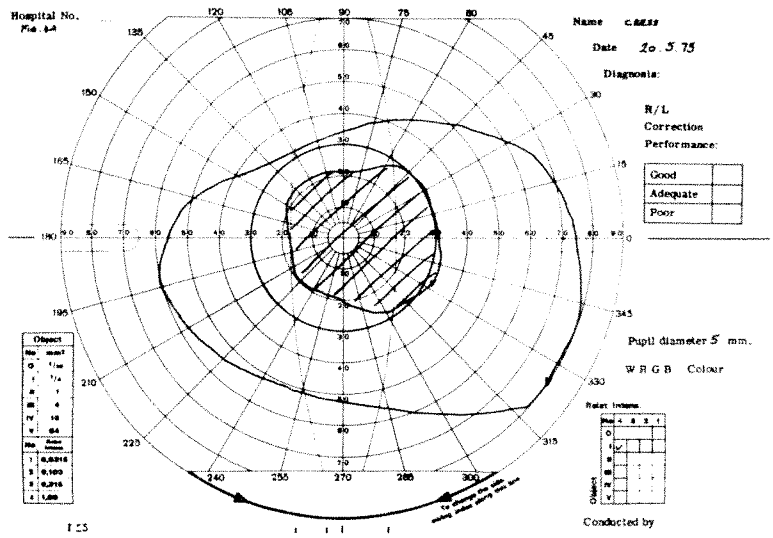


Fig. 6*a* *Visual field in macular oedema type of CRVO with large central scotoma*

DISC AND RETINAL NEOVASCULARISATION

No disc or retinal new vessels were found in the non-ischaemic type of occlusion at any time of the follow-up.

Two out of the 12 treated eyes with the ischaemic type of occlusion had disc new vessels at the time of treatment (Table 2). In one eye the new vessels disappeared, the other progressed to more fibrosis and a traction retinal detachment of the upper temporal quadrant. At the time of treatment preretinal neovascularisation was found in 1 eye (Fig. 10*a*). In this case new vessels disappeared after

Table 2 *Neovascular complication after 1 year follow-up in ischaemic type of CRVO*

	Treated group	*Untreated group*
Number of cases	*12*	*11*
Rubeosis iridis without glaucoma	3	4
Neovascular glaucoma	—	2
Disc new vessels	1	5
Preretinal new vessels	3	2
Vitreous haemorrhage	1	—

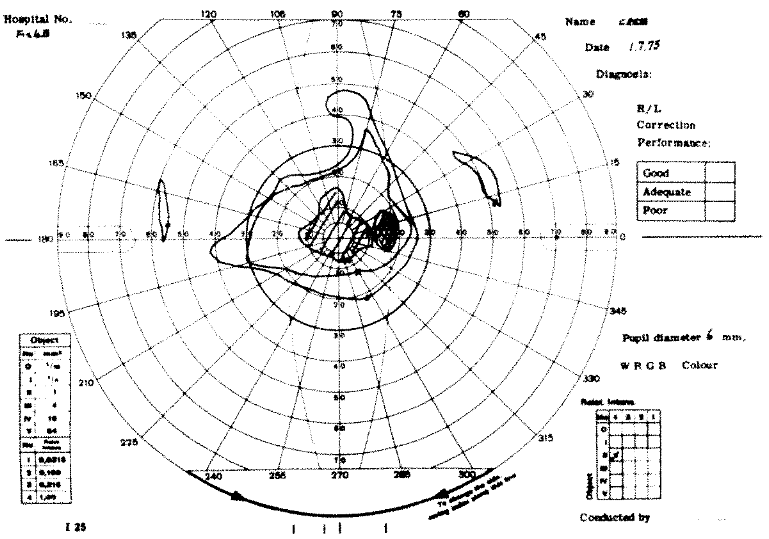
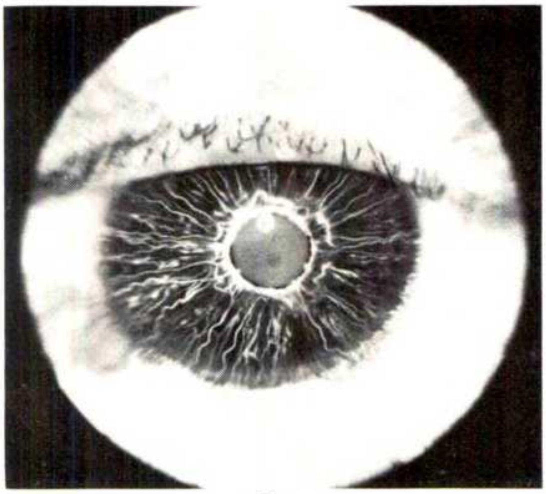


Fig. 6*b* *Same as Fig. 6*a *but after panretinal photocoagulation showing decrease in central scotoma, but considerable constriction of peripheral field*



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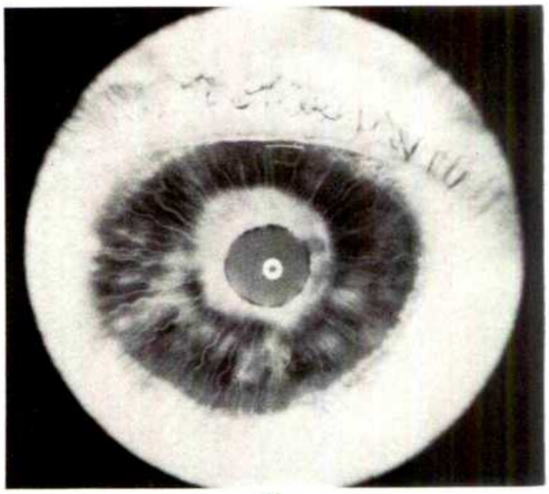

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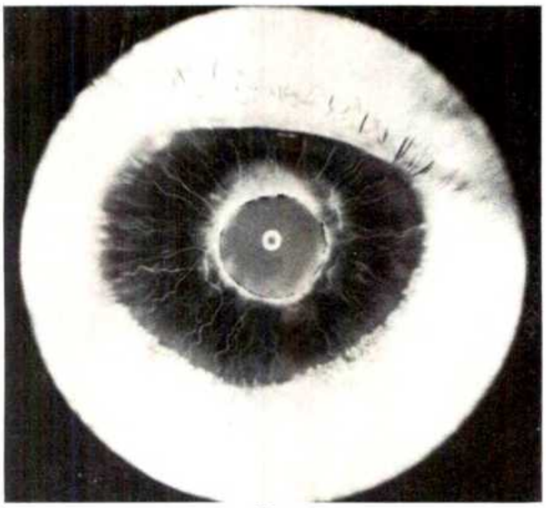


7c

Fig. 7*a* and *b* *Ischaemic type of CRVO. Pretreatment iris fluorescein angiogram showing mild neovascularisation and leakage of dye*

Fig. 7*c* *Same as Fig.* 7a *and* b, *but 1 month after panretinal photocoagulation. Iris new vessels improved markedly*

treatment (Fig. 10*b*). In 2 eyes these new vessels remained small along the main temporal vein and disc (Fig. 11), but in 1 eye preretinal neovascularisation has resulted in vitreous haemorrhage.

In the untreated group 5 out of the 11 eyes with the ischaemic type of occlusion have developed disc new vessels (Fig. 9*b*), resulting in secondary traction detachment of the retina in 2. In the other 3 cases disc new vessels remained small and have not caused any further complications yet. All but one of the 5 eyes with disc new vessels developed iris new vessels (Fig. 9*a*, *b*), but only one developed neovascular glaucoma. In 2 of the 11 untreated eyes preretinal neovascularisation was found (Fig. 12); one of these developed disc new vessels as well. There were no vitreous haemorrhages from the new vessels in the untreated eyes during the period of follow-up.

Table 2 summarises the occurrence of all the neovascular complications after 1 year follow-up in the 12 treated and 11 untreated cases of the ischaemic type of occlusion. Because of the small number of cases the differences are not statistically significant, although it seems that neovascular glaucoma and disc neovascularisation were more common in the untreated eyes, whereas preretinal new vessels were equally common in the treated and untreated groups.

MACULAR FINDINGS

At the onset of the study some macular oedema with or without cystoid spaces and haemorrhages was

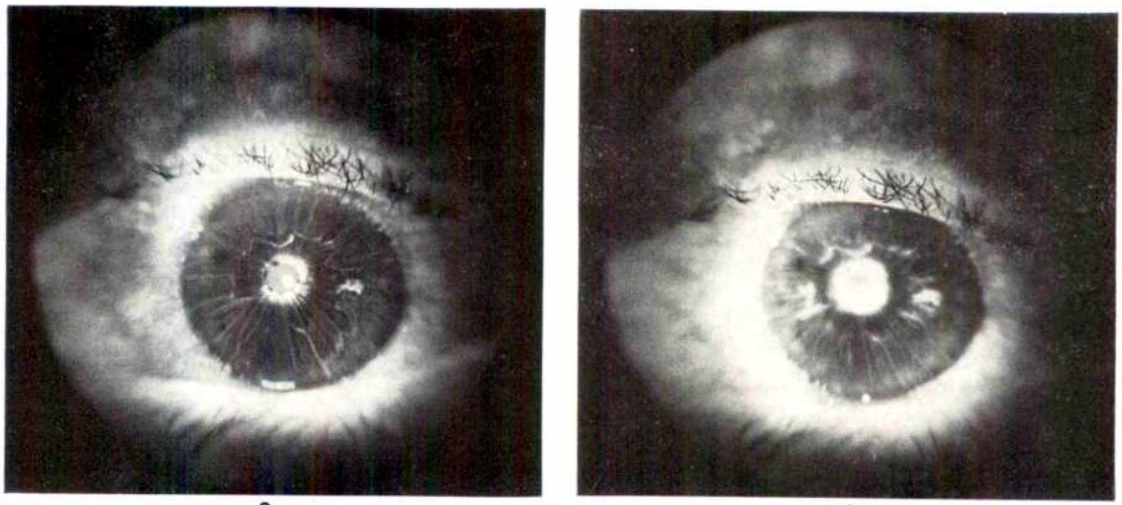

8a 8b

Fig. 8*a* and *b* *Ischaemic type of CRVO, untreated eye. Mild iris neovascularisation at entry into the trial*

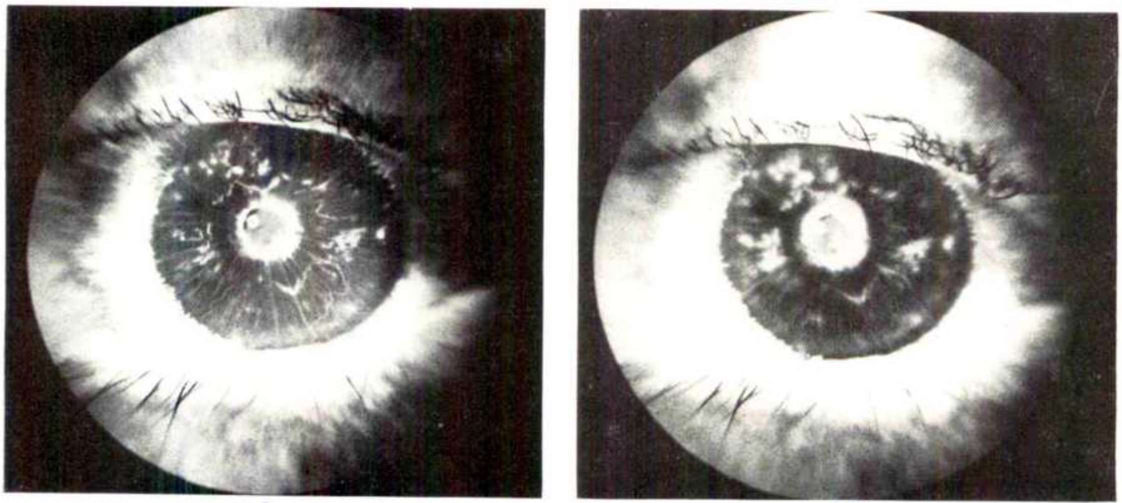

8c 8d

Fig. 8*c* and *d* *Same as Fig.* 8a *and* b, *but after 3 months' follow-up showing progression of the iris neovascularisation*

present in all cases. Table 3 summarises the final macular appearance in the various groups.

Macular changes in the 'non-ischaemic' type of occlusion were universal: in all the 12 treated eyes macular oedema decreased, but in 5 of them cystoid macular oedema persisted (Fig. 13, *a*, *b*, *c*) and in one eye a macular hole developed. In the other 6 eyes pigment epithelial changes and retinal atrophy appeared (Fig. 14, *a*, *b*, *c*). Some decrease in macular oedema was also seen in all 13 untreated cases, but cystoid macular changes remained in 9 eyes. In 5 out of 13 untreated cases the macula became dry and pigment epithelial changes and retinal atrophy developed.

Macular changes also occurred in the ischaemic type of occlusion. In 2 out of 12 treated eyes macular oedema persisted, and in 6 eyes the macula became dry with pigment epithelial changes or subretinal scarring (Fig. 15). In 2 eyes preretinal fibrosis and macular traction developed (Fig. 16). One macula looked normal (in this case capillary closure did not affect the macular area), and in 1 eye the fundus could not be seen because of vitreous haemorrhage. In 3 out of 11 untreated eyes with the ischaemic type

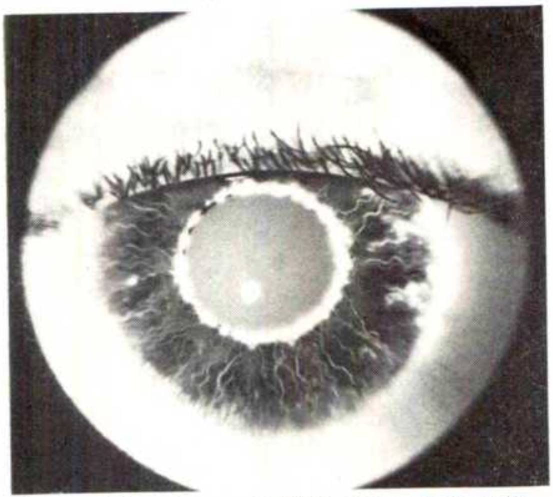


Fig. 9*a* *Ischaemic type of CRVO untreated eye. Mild rubeosis iridis*

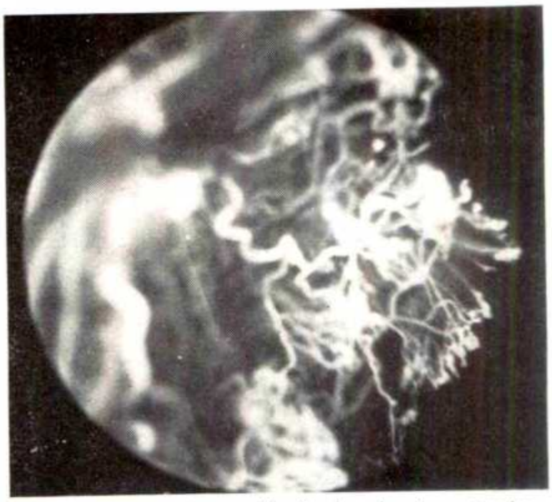


Fig. 9*b* *Same patient as Fig.* 9a, *but showing extensive new vessels formation on optic disc*

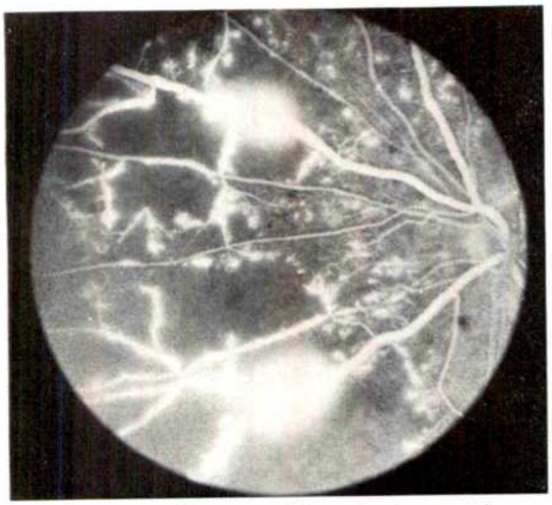


Fig. 10*a* *Preretinal new vessel formation in eye with extensive capillary closure in the nasal field*

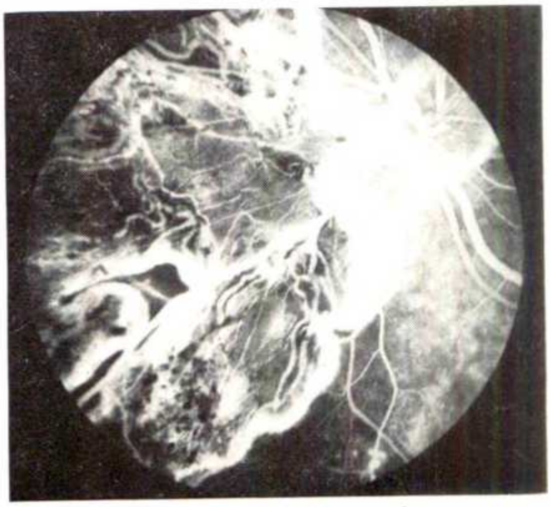
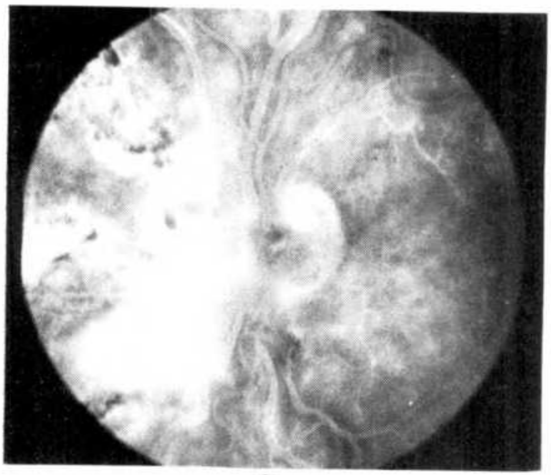


Fig. 10*b* *Same as Fig.* 10a, *but 1 year after photocoagulation of the non-perfused area, new vessels have regressed*

Table 3 *Macular appearance after 1 year follow-up in 24 treated and 24 untreated cases of CRVO*

Macula	*Treated group*		*Untreated group*	
	Non-ischaemic type of CRVO	*Ischaemic type of CRVO*	*Non-ischaemic type of CRVO*	*Ischaemic type of CRVO*
Total number of eyes	*12*	*12*	*13*	*11*
Normal	—	1	—	—
Oedematous	5	2	9	3
Pigment epithelial changes and/or retinal atrophy	7	6	4	4
Preretinal fibrosis	—	2	—	1
Not visible (vitr. haem., neovas. glaucoma)	—	1	—	3



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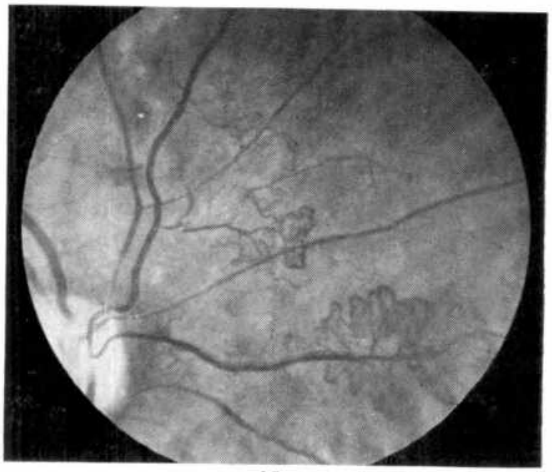

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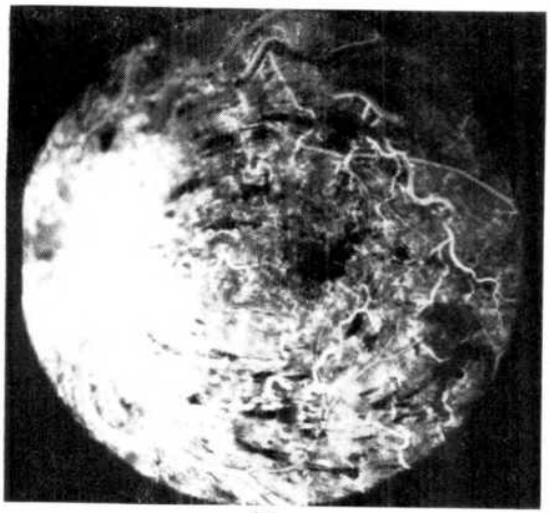


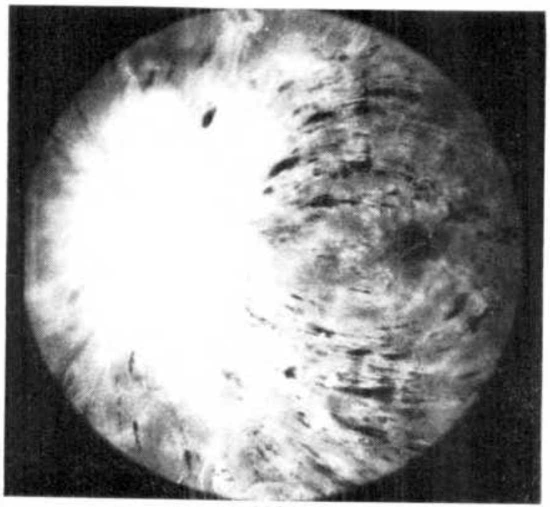
13a

Fig. 11 *Ischaemic CRVO. Small new vessels on optic disc developed in spite of photocoagulation*

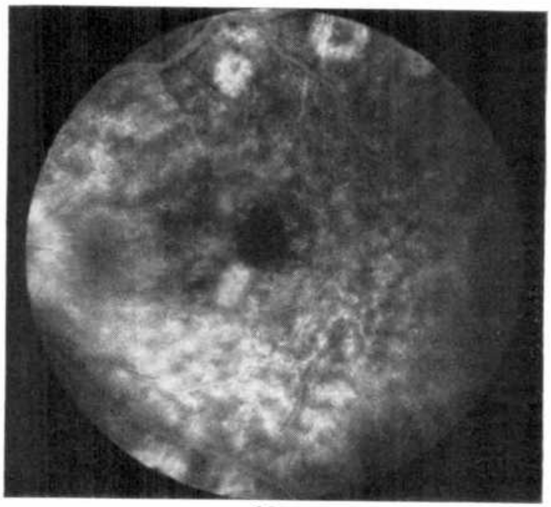
Fig. 12 *Ischaemic CRVO, untreated eye. Several preretinal new vessels visible*

Fig. 13*a* and *b* *Hyperpermeability type of CRVO. Pretreatment fluorescein angiograms with broken perifoveal capillary arcade and leakage of dye*

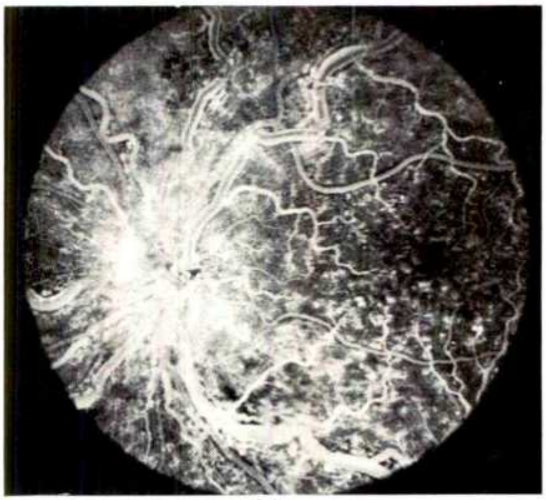
Fig. 13*c* *Same as Fig. 13*a *and* b, *but 1 year after photocoagulation with persistent fluorescein leakage and macular oedema*



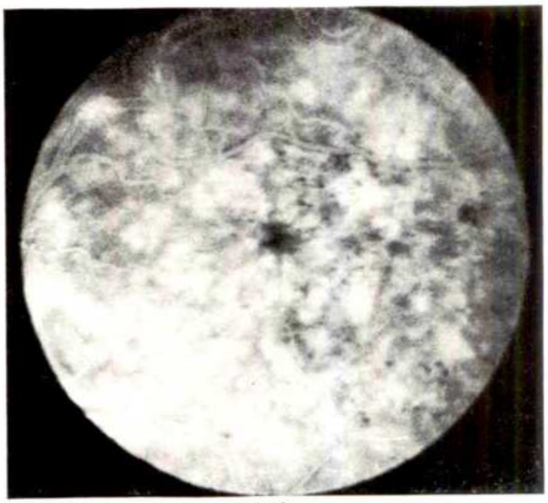
13b



13c



14a



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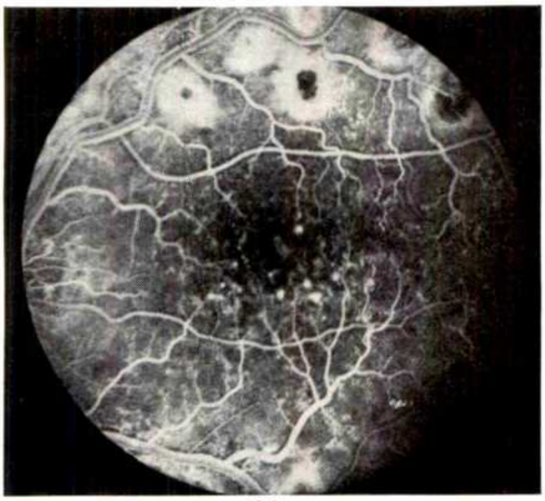

14c

Fig. 14*a* and *b* *Hyperpermeability type of CRVO. Pretreatment fluorescein angiogram with broken perifoveal capillary arcade and leakage of dye*

Fig. 14*c* *Same as Fig. 14*a *and* b*, but 1 year after photocoagulation. Macula dry with marked pigment changes*

of occlusion diffuse macular oedema with or without cystoid spaces persisted throughout the follow-up, whereas in 4 eyes the macula became dry and atrophic with marked pigment epithelial changes and 1 case developed macular traction due to preretinal fibrosis. In 1 eye the macula was covered by large fronds of new vessels (Fig. 9*b*), and in 2 eyes, which developed neovascular glaucoma, the macula was not clearly visible at the latest examination.

Discussion

In a previous paper (Laatikainen and Kohner, 1976) we have shown that in the ischaemic type of CRVO prognosis is always poor. In those with the hyperpermeability response macular oedema from dilated and leaky capillaries is the cause of visual loss.

In the ischaemic type of occlusion large areas of retina are non-perfused. In CRVO as in other vascular retinopathies retinal non-perfusion acts as a stimulus for neovascularisation. Therefore the rationale for photocoagulation therapy is to destroy non-perfused retina or at least reduce it. In these eyes the visual prognosis did not improve by photocoagulation, but the development of late neovascular complications, particularly rubeosis iridis, neovascular glaucoma, and probably disc neovascularisation, were reduced or prevented by panretinal photocoagulation. In some eyes photocoagulation also caused fundus and iris new vessels to regress. This was also noticed in a few cases of neovascular glaucoma, which were not included in this study but

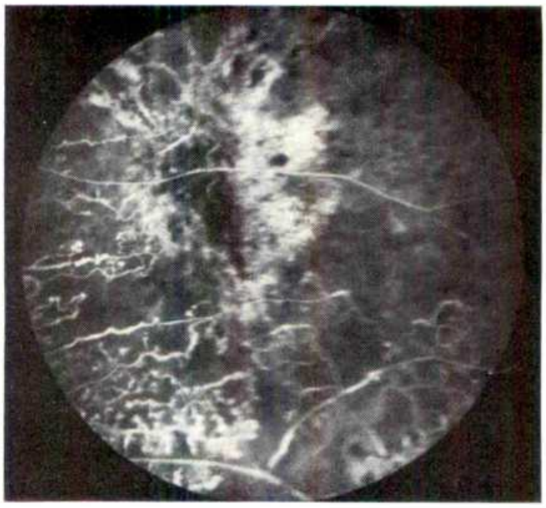

Fig. 15 *Ischaemic CRVO. Avascular atrophic macula with subretinal scarring 1 year after photocoagulation, over 500 peripheral burns*

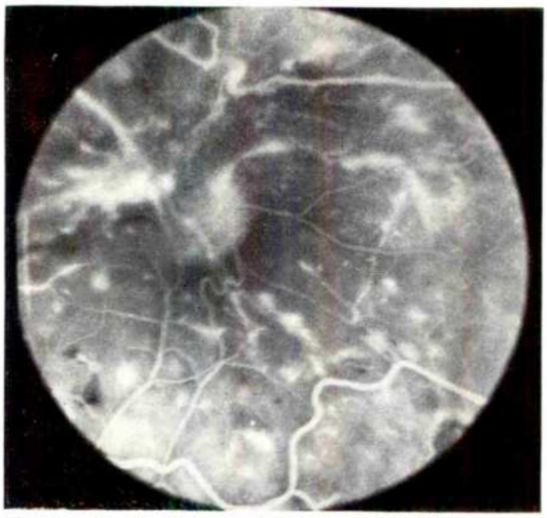

Fig. 16 *Fundus photograph in ischaemic CRVO, massive preretinal fibrosis and traction on the macula developed after photocoagulation*

which were similarly treated by xenon arc panretinal photocoagulation (Laatikainen, 1977).

Results of this study are in accordance with the preliminary results reported by May *et al.* (1976). In their randomised study on 20 eyes (10 treated, 10 untreated) 2 cases of neovascular glaucoma were found in the untreated group and none in the treated group. Theodossiadis (1976) also had 3 cases of neovascular glaucoma in the group of 18 untreated eyes and none in the group of 25 treated eyes, but this study was not randomised. However, the number of cases with the ischaemic type of occlusion and therefore in danger of developing neovascular glaucoma is not known in these two studies.

The rationale for photocoagulation therapy in the non-ischaemic type of CRVO is to obliterate leaking capillaries, thereby enabling reduction of the retinal oedema. The area of capillary damage may, however, be extensive and all the leaking capillaries cannot be photocoagulated, because the central macular area must be spared. It has also been suggested that by reducing the area of the viable retina by photocoagulation nourishment of the remaining retina might be improved (Campbell and Wise, 1973).

In this study the treatment was performed outside the temporal vascular arcade only, so that direct photocoagulation of the macular capillaries was not done. After 1 year follow-up the percentage of dry maculae was greater in the treated than in the untreated group; however, there was no difference in the central visual acuity between the treated and untreated eyes. It could be argued that treatment should have been inside the temporal arcade. However, in retinal branch vein occlusion Shilling (in press) found no difference between treated and untreated eyes, although he treated leaking vessels in the perimacular region using the laser.

The final visual outcome of both treated and control groups was in accordance with our earlier studies of untreated cases of non-ischaemic CRVO with macular oedema, which showed little change after the 3-month examination. No significant improvement in visual acuity in spite of drying out of the macular oedema was found either by Theodossiadis (1976) or May *et al.* (1976).

The duration of symptoms before treatment obviously influences final prognosis, because in the non-ischaemic type of CRVO spontaneous improvement during the first 3 months is common. Therefore in this study only eyes with a poor tendency to spontaneous recovery were included. Permanent macular damage may have resulted from the long period of macular oedema, and earlier treatment may produce better results.

In the non-ischaemic type of CRVO serious irreversible changes are usually restricted to the macular area. Therefore the peripheral visual field is usually not constricted. In those eyes the marked constriction of the fields caused by panretinal photocoagulation should be regarded as an unfavourable result of treatment.

On the basis of this study it is suggested that panretinal photocoagulation should be considered in cases with the ischaemic type of CRVO in order to prevent late neovascular complications, and in these eyes the treatment should be done as early as possible. On the other hand panretinal photocoagulation seems to have no value regarding visual prognosis in cases with the nonischaemic type of occlusion and macular oedema.

We are grateful to all consultants at Moorfields Eye Hospital who referred patients to us.

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Complicated retinal detachment and its management with pars plana vitrectomy

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SUMMARY Fifty patients with retinal detachment accompanied by vitreous haemorrhage, perforating eye injuries, intraocular foreign bodies, massive preretinal retraction, giant tears greater than 180°, and proliferative retinopathies underwent pars plana vitrectomy, cryocoagulation, scleral buckling, and intravitreal gas injection. Intraoperative complications included minimal to moderate bleeding and iatrogenic retinal tears, but no retinal dialysis was produced at the pars plana sclerotomy site. Postoperative complications included recurrent vitreous haemorrhage, rubeosis, haemolytic, erythroclastic, or neovascular glaucoma, transient increase of intraocular pressure, uveitis, and macular pucker. Phthisis bulbi occurred in 6 eyes; in 3 of these eyes enucleation was required. Successful reattachment was accomplished in 56% of these complicated retinal detachments, most of which had been considered inoperable by conventional techniques. Visual improvement was achieved in 46% of eyes. Follow-up ranged from 6 to 29 months.

The difficulty involved in managing retinal detachment accompanying vitreal opacities and bands has been recognised in cases including traumatic eye injuries (Johnston, 1971; Percival, 1972), proliferative retinopathies (Blach, 1975; Goldberg, 1971), vitreous haemorrhage obscuring the fundus view, and so-called massive preretinal retraction (MPR) (Cockerman *et al.*, 1970) or massive periretinal proliferation (MPP) (Machemer and Laqua, 1975). These 'complicated' cases were often considered to be inoperable, and the success rate prior to the pars plana vitrectomy approach was discouraging. With the advent of this technique it has been felt that removal of vitreous opacities as part of the retinal detachment surgery might improve the prognosis (Machemer and Norton, 1975; Peyman *et al.*, 1975a, b).

This report describes our experience with 50 consecutive patients who had 'complicated' retinal detachments operated on at the University of Illinois Eye and Ear Infirmary.

Subjects and methods

Selection of patients and their preoperative evaluation are described elsewhere (Peyman *et al.*, 1976). Procedures included indirect ophthalmoscopy, biomicroscopy with three-mirror Goldman contact lens where feasible, ultrasonography, and bright-flash intensity electroretinography in some cases.

The basic surgical technique is described in previous reports (Peyman *et al.*, 1975a, b; Peyman and Huamonte, 1975). It involves the following methods:

(1) Removal of opaque vitreous, including vitreous bands and membranes, with the vitrophage. Vitreous scissors and forceps (Peyman and Huamonte, 1976) were used in only 2 cases for bands too tough to be engaged with the vitrophage and for extraction of intraocular foreign bodies.

(2) Localisation of retinal breaks through clear media.

(3) Placement of a silicone plate as an exoplant with an encircling band and drainage of subretinal fluid (Fig. 1). Silicone sponge was also used as an exoplant.

(4) Exchange of fluid for gas (Fig. 2). Disposable needles, 25 and 27 gauge, were attached to 10 ml syringes, then introduced simultaneously through the pars plana about 180° apart into the vitreous cavity. The syringe with the 25 gauge needle served to aspirate the intraocular fluid, while the syringe with the 27 gauge needle was used to inject air or gas. The intraocular pressure did not exceed 30 mmHg at the end of surgery. Air alone was used in 3 eyes; and air-gas mixture or pure gas was used in 40 eyes. Either sulphur hexafluoride or octafluorocyclobutane was chosen arbitrarily for gas

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injection. No air or gas was injected in 7 eyes. Patients with giant tears were placed in a prone position prior to exchange of fluid for gas.

(5) Cryocoagulation of retinal breaks. If retinal breaks could not be detected, a 360° cryocoagulation in 1 or 2 rows was performed prophylactically under the band.

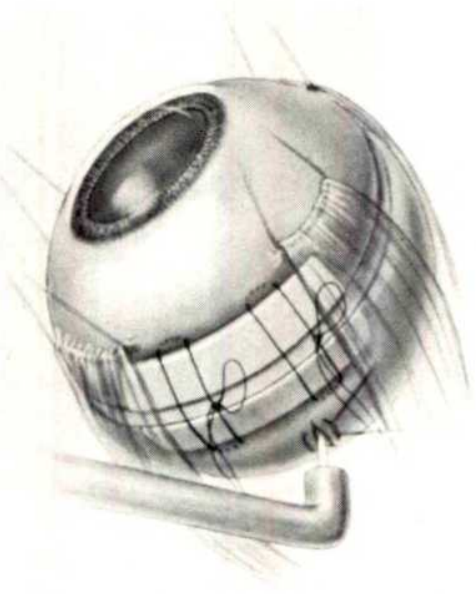


Fig. 1 *Encircling band and silicone plate as an exoplant. Drainage of subretinal fluid*

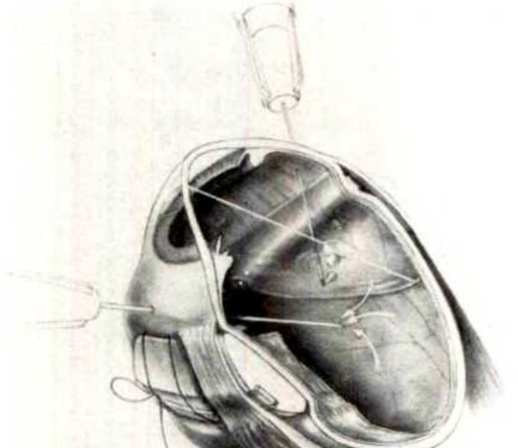


Fig. 2 *Exchange of intravitreal fluid for gas with two syringes attached to disposable 25 and 27 gauge needles*

Indications for this combined procedure included retinal detachment accompanied by opaque ocular media, vitreous body organisation with bands and membranes, perforating eye injuries, and severe MPR that developed after multiple unsuccessful retinal detachment operations. These cases were considered inoperable by conventional scleral buckling procedures.

Follow-up ranged from 6 to 29 months with a mean of 11 months. Anatomical success was achieved if the retina was attached for a minimum of 6 months after surgery, and anatomical failure was defined as incomplete reattachment of the retina after retinal and vitreous surgery.

Results

The cases are grouped according to their prime aetiological factor. Results of visual acuity and anatomical success or failure are categorised in Table 1. A classification based on degree of improvement of visual acuity has been reported previously (Peyman *et al.*, 1976) (see Table 2) and was used in our data analysis. Results of surgical, postoperative, and late complications after vitrectomy are categorised in Table 3.

Group 1—Vitreous haemorrhage or opacities accompanying retinal detachment. Six eyes are included in this group—5 with vitreous haemorrhage and 1 with retropupillary membrane and vitreous haemorrhage. Duration of detachment before surgery ranged from 1 to 2 months; in 1 patient the time was undetermined. 5 eyes showed visual improvement postoperatively. For 1 patient the operation was an anatomical failure (MPR), but visual acuity remained unchanged. In 1 patient a retinal tear that was sustained during the operation was cryocoagulated. Macular pucker was detected during surgery in 1 eye. Postoperatively, transient corneal oedema was seen in 3 eyes and macular pucker was observed in 2. Follow-up ranged from 6 to 19 months (mean, 11 months).

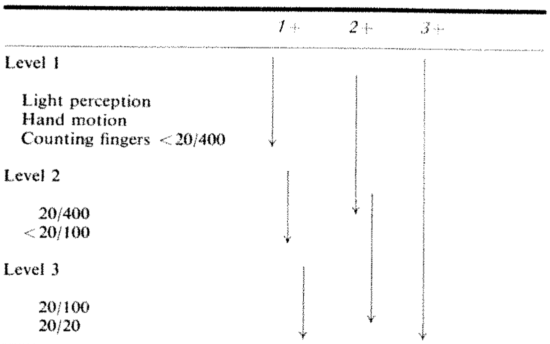
Group 2—Traumatic retinal detachment due to perforating injuries with and without retained foreign bodies. Part of this group was reported previously (Peyman *et al.*, 1975a). A total of 14 eyes were operated on—5 eyes with intraocular foreign bodies, 5 injured with sharp perforating objects, 2 with scleral rupture, and 2 with corneoscleral laceration of undetermined origin. The interval from time of injury to vitrectomy varied from hours to 15 years. In 2 eyes pre-existing macular scar was detected at surgery. Visual acuity improved in 7 eyes, remained unchanged in 3, and became worse in 4. Anato-

Table 1 *Visual and anatomical results after vitrectomy*

Diagnosis	*No. of eyes*	*Visual improvement*			*Vision unchanged*	*Vision worse*	*Others**	*Anatomical results*	
		3+	*2+*	*1+*				*Success*	*Failure*
Group 1 Vitreous haemorrhage and media opacification	6	2 (33%)	2 (33%)	1 (17%)	1 (17%)	0	0	5 (83%)	1 (17%)
Group 2 Trauma; perforating injuries									
(a) With intraocular foreign bodies	5	1 (20%)	1 (20%)	0	3 (60%)	0	0	3 (60%)	2 (40%)
(b) Without intraocular foreign bodies	9	2 (22%)	1 (11%)	2 (22%)	0	4 (45%)	0	6 (67%)	3 (33%)
Group 3 Massive preretinal retraction	13	0	2 (15%)	3 (23%)	4 (31%)	2 (15%)	2 (15%)	7 (54%)	6 (46%)
Group 4 Giant retinal tears greater than 180°	4	0	1 (25%)	0	1 (25%)	2 (50%)	0	1 (25%)	3 (75%)
Group 5 Proliferatives retinopathies									
(a) With rhegmatogenous retinal detachment	4	1 (25%)	2 (50%)	1 (25%)	0	0	0	4 (100%)	0
(b) With tractional retinal detachment and massive fibrous proliferation	9	0	0	1 (12%)	4 (44%)	4 (44%)	0	2 (22%)	7 (78%)
Total	50	6 (12%)	9 (18%)	8 (16%)	13 (26%)	12 (24%)	2 (4%)	28 (56%)	22 (44%)

*Mental retardation in 2 patients prevented measurement of visual acuity but the retina was re-attached

Table 2 *Classification of visual acuity improvement after vitrectomy*



	1+	*2+*	*3+*
Level 1			
Light perception Hand motion Counting fingers <20/400			
Level 2			
20/400 <20/100			
Level 3			
20/100 20/20			

1+ Indicates improvement within any level; 2+ improvement to the next better level; and 3+ improvement from level 1 to level 3

mical success was accomplished in 9 eyes. Postoperative complications included the following: transient elevation of introcular pressure (IOP), 4 eyes; transient corneal oedema, 4 eyes; rubeosis, 1 eye; and macular pucker, 2 eyes. Enucleation was required in 2 eyes because of phthisis bulbi and fear of sympathetic ophthalmia. Follow-up was from 6 to 29 months (mean, 13 months).

Group 3—Massive preretinal retraction. A total of 13 eyes were operated on in this group. Anatomical success was achieved in 7 eyes and visual acuity improved in 5 eyes. Visual acuity could not be determined in 2 patients as they have severe mental retardation. Only 1 significant intraoperative complication occurred: this was one retinal tear that was cryocoagulated and caused no retinal separation postoperatively. Postoperative complications included vitreous haemorrhage in 2 eyes, which cleared with conservative measures; transient elevation of IOP in 3; transient corneal oedema in 5; development of macular pucker in 2; and phthisis in 1. In addition severe uveitis with sterile hypopyon, which responded to medical therapy, was observed in 1 eye, and pigment migration to the macular area was observed in another eye. Follow-up ranged from 6 to 14 months (mean, 10 months).

Group 4—Giant retinal tears greater than 180°. A total of 4 eyes were operated on; preoperatively 2 of these eyes had severe preretinal organisation. In only 1 eye was the retina successfully reattached with resultant visual improvement. Of the remaining 3 eyes the vision was unchanged in 1 and worsened in 2. There were no intraoperative complications. Postoperatively 1 eye developed vitreous haemorrhage and haemolytic or erythroclastic glaucoma and eventually became phthisical; 1 eye progressed to

Table 3 *Surgical, postoperative, and late complications following vitrectomy of retinal detachments**

		Surgical complications				*Postoperative and late complications*										
Diagnosis	*Number of eyes*	*Minimal bleeding with clearing*	*Moderate bleeding, clearing with lavage*	*Cataract*	*Retinal tear at surgery*	*Haemorrhage*	*Haemolytic or erythroclastic, and neovascular glaucoma*	*Transient increase in intraocular pressure*	*Bullous keratopathy*	*Transient corneal oedema*	*Cataract*	*Severe uveitis*	*Rubeosis*	*Macular pucker*	*Tractional retinal detachment or massive preretinal retraction*	*Phthisis*
Group 1 Vitreous haemorrhage and media opacification	6	0	1 (17)	0	1 (17)	1 (17)	0	0	0	3 (50)	0	0	0	2 (42)	1 (17)	0
Group 2 Trauma: secondary to perforating injuries	14	2 (14)	1 (7)	0	0	0	0	4 (29)	0	4 (29)	0	0	1 (7)	2 (14)	2 (14)	2 (14)
Group 3 Massive preretinal retraction	13	0	0	0	1 (8)	2 (15)	0	3 (23)	0	5 (38)	0	1 (8)	0	2 (15)	0	1 (8)
Group 4 Giant retinal tears >180°	4	0	0	0	0	1 (25)	1 (25)	0	0	1 (25)	0	0	0	0	1 (25)	1 (25)
Group 5 Proliferative retinopathies																
(a) With rhegmatogenous retinal detachment	4	1 (25)	1 (25)	1 (25)	2 (50)	1	0	0	0	3 (75)	1 (25)	1 (25)	0	1 (25)	0	0
(b) With tractional retinal detachment and massive fibrosis proliferation	9	1 (11)	1 (11)	0	1 (11)	1 (11)	3 (33)	0	2 (22)	3 (33)	0	0	3 (33)	0	2 (22)	2 (22)
Total	50	4 (8)	4 (8)	1 (2)	5 (10)	6 (12)	4 (8)	7 (14)	2 (4)	19 (38)	1 (2)	2 (4)	4 (8)	7 (14)	6 (12)	6 (12)

*Each complication is considered individually. Figures in parentheses are percentages

end-stage MPR. Follow-up ranged from 7 to 12 months (mean, 9 months).

Group 5—Proliferative retinopathies: A total of 13 eyes had proliferative retinopathies of different aetiology including diabetes, sickle cell disease, and sarcoidosis. This category was subdivided into 2 groups:

(1) *Rhegmatogenous detachment with vitreous traction:* These eyes had moderate to severe vitreous haemorrhage or opacities, traction bands, and retinal breaks. A total of 4 eyes were operated on: 2 corresponded to sickle cell retinopathy and 2 to diabetic retinopathy, both with early fibrovascular proliferation. In 4 eyes the retina was reattached and visual acuity improved in all. Retinal tears were created in 2 eyes during surgery. These were cryocoagulated and no retinal detachment was noted postoperatively. A cataract was created intraoperatively that was removed at the time of vitrectomy. Postoperatively 1 eye developed macular pucker and another had severe uveitis. One patient developed posterior subcapsular cataract.

(2) *Tractional detachment with massive fibrovascular proliferation with no retinal holes:* This group included 9 eyes, 8 of which were diabetic. Each had severe fibrous proliferation and fibrovascular stalk arising from the disc. Peripapillary tractional retinal detachment involving the macular area was caused by the extensive fibrovascular tissue. The nondiabetic case was a patient with sarcoidosis accompanied by fibrovascular proliferation, preretinal organisation, and long-standing retinal detachment, for which multiple procedures previously had failed to reattach the retina. Visual acuity improved in 1 eye, was unchanged in 4, and became worse in 4. Anatomical success was achieved in 2. A retinal tear was created in 1 eye that was cryocoagulated intraoperatively; eventually tractional retinal detachment worsened in this eye.

Major postoperative complications included haemolytic, erythroclastic, or neovascular glaucoma and corneal oedema. Two eyes became phthisical and 1 of them was enucleated for intractable severe pain. In 1 eye, which had additional panretinal cryocoagulation performed during surgery, moderate exudative retinal detachment was observed postoperatively. This reabsorbed spontaneously at the end of the second postoperative week. Follow-up ranged from 8 to 18 months (mean, 11 months).

Discussion

Although conventional buckling operations are most often employed to reattach the retina in the great majority of retinal detachment cases, these techniques are not usually successful if the fundus view is obscured and vitreous opacities are present, and if severe vitreo-retinal traction or preretinal organisation exists. For these complicated situations newly developed methods and techniques of vitreous removal can make the eyes operable (Machemer and Norton, 1975; Peyman *et al.*, 1975 a, b; Peyman and Huamonte, 1975; Benson and Machemer, 1976, Hutton *et al.*, 1976; Peyman *et al.*, 1976; Peyman and Huamonte, 1976).

In our series the complicated retinal detachment cases were separated into 5 groups according to the prime associated condition and cause: vitreous haemorrhages, trauma, giant retinal tears greater than 180°, massive preretinal retraction (MPR), and tractional and rhegmatogenous detachment accompanying proliferative retinopathies.

Group 1: Conservative measures such as bilateral patching and bed rest are important to clear the vitreous body preoperatively when a haemorrhage obscures the fundus view. In spite of these procedures vitreous haemorrhage can persist and no clearing is achieved. However, there is a limitation between the time that a detachment is discovered and when the surgery should be performed. It has been demonstrated that surgical management of a retinal detachment involving the macula for longer than 8 weeks has poor prognosis for recovery of visual function (Grupposo, 1975). If the surgery is performed without a long delay, the visual outcome should be better. Therefore removal of vitreous haemorrhage or opacities which have not reabsorbed within 2 to 4 weeks is considered important for successful management of rhegmatogenous retinal detachment. Our results indicate a reasonably good prognosis in this group of cases.

Group 2: Perforating eye injuries are often accompanied by vitreous haemorrhage damage of the vitreous, retina, and uvea, and intraocular foreign body in the acute stage. Later, fibrous ingrowth and retinal detachment often complicate these situations. In the past the cure rate for these disrupted eyes associated with retinal detachment ranged from 12 to 16% (Johnston, 1971; Percival, 1972) but the use of vitrectomy and of new surgical techniques has improved the prognosis in injured eyes (Peyman *et al.*, 1975a; Benson and Machemer, 1976; Hutton *et al.*, 1976; Mandelcorn, 1977) from 40 to 60%. In our series we were successful in reattaching the retina in 64% of eyes. We believe that early management is extremely important to remove the vitreous haemorrhage, to seal the retinal tears, and to eliminate the situation that ordinarily results in fibrovascular ingrowths, cyclitic membranes, ciliary body detachments, retinal detachments, and massive preretinal organisation.

Group 3: Massive preretinal retraction has been a sombre complication of retinal detachment surgery, and it continues to present a difficult and challenging problem. The advent of vitrectomy and gases that expand and reabsorb slowly can possibly afford a better outcome for these eyes. In our cases vitrectomy has been used to remove many of the bridging bands and membranes, mobilising in this way the immobile retina. In addition the mechanical expansion of the gas can tamponade the retina smoothly against the buckle (Fig. 3). Buckling is an important step in releasing traction of thick preretinal membranes located at the equator, membranes that are inseparable from the retina by mechanical means. (Peeling of epiretinal membranes

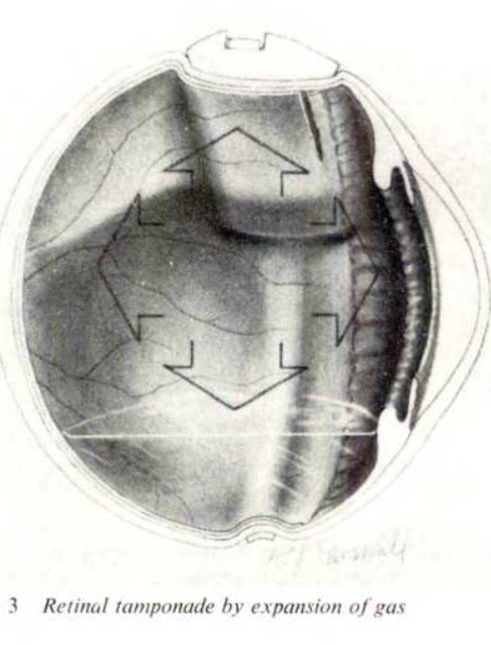


Fig. 3 *Retinal tamponade by expansion of gas*

was performed in only 3 cases.) In other series, when MPR was treated with silicone oil injection and scleral buckling, the success rate ranged from 9% (Cockerman *et al.*, 1970) to 62% (Cibis *et al.*, 1962). The usefulness of intravitreal silicone oil injection, however, has been questioned because of the long-term sequelae such as corneal degeneration, cataracts, and retinal degeneration. In our group of patients with MPR we were successful in reattaching 54% of the retinas. Most of these eyes with MPR had had multiple unsuccessful buckling operations prior to treatment with our combined technique.

Group 4: For patients with giant retinal tears greater than 180° the results were not very satisfactory. Two of these cases were accompanied by severe preretinal organisation. In other series the success rates were 14% (Schepens and Freeman, 1967), 25% (Norton *et al.*, 1969), and 43% (Machemer and Allen, 1976).

Group 5: Eyes having proliferative retinopathy and rhegmatogenous retinal detachment are clearly helped by the combined procedure of vitrectomy and buckling. Holes that were missed because of vitreous opacities were easily detected after removal of vitreous. Most of these cases had minimal to moderate proliferative changes accompanied with vitreous haemorrhage and opacities. In one series of similar cases (Gragoudas and McMeel, 1976) the authors reported retinal reattachment by routine buckling procedures in 74% of eyes, but cases with undetected breaks or poor visibility of the fundus were excluded. In our series 4 eyes with these last characteristics were all successfully reattached.

In the end-stage proliferative retinopathies with massive fibrous proliferation our results have not been encouraging. Only in 2 cases out of 9 was anatomical success achieved. It is important to state that proliferative retinopathies with tractional detachment surrounding the disc have had the worst prognosis among our patients. The precise time to operate on these patients, either before or after detachment of the macula, has not been clearly decided. In the past we have operated only when the macula has already been detached. Further observations need to be made to determine whether an early operation will prevent irreversible deterioration of vision or not.

Intraoperative complications encountered in our series included minimal to moderate bleeding, which was usually stopped by raising the IOP; intraocular diathermy was not commonly required. Iatrogenic retinal tears occurred in 5 cases (10%), a relatively high incidence if they are compared with the 2% incidence in our overall pars plana vitrectomy series (Peyman *et al.*, in press). These tears were produced when vitreoretinal traction was attacked at the vitreous base or at the equator and, consequently, more manipulation was required. This is exemplified in patients with sickle cell retinopathy.

No retinal dialysis was produced at the pars plana sclerotomy in any of our cases. The absence of this complication might be explained by the length of the sclerotomy (4 mm), which permits the smooth passage of the vitrophage and avoids forcing the vitrectomy instrument into the eye. Also, it might be explained by the linear oscillation of our instrument and the fact that we did not use fibroptic bundles in any of these cases.

Postoperatively 1 eye showed exudative retinal detachment which had had panretinal cryocoagulation during vitrectomy, a complication that has been described with other types of energy (Huamonte *et al.*, 1976). Exudation was noted the second day after vitrectomy and reabsorption occurred at the end of the second week without any additional intervention.

We noticed a higher incidence of neovascular glaucoma and fresh rubeosis in the group of patients with severe fibrovascular proliferation. Most of these patients were diabetic and had advanced retinal vasoproliferation. Macular pucker was also observed in some of our patients. This was possibly due to multiple operations before vitrectomy or the magnitude of the surgery, or to other undetermined factors.

The overall anatomical success rate in our patients was 56%. Visual acuity improvement was achieved in 46%.

The combined technique of pars plana vitrectomy, scleral buckling, release of subretinal fluid, and intravitreal gas injection thus appears to offer a better chance for otherwise inoperable, 'hopeless' eyes than is at present afforded by routine procedures. This radical type of surgery should be performed only in extreme cases of retinal detachment where conventional techniques have failed or are virtually certain to fail.

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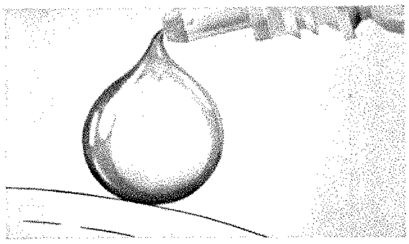

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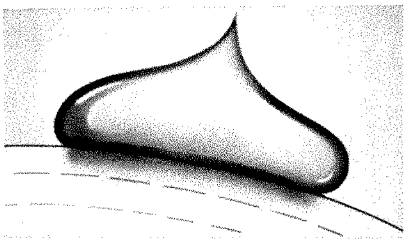

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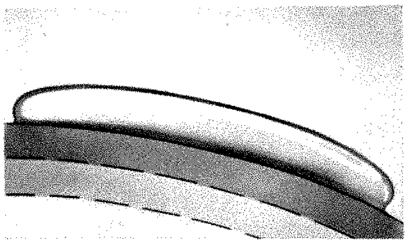

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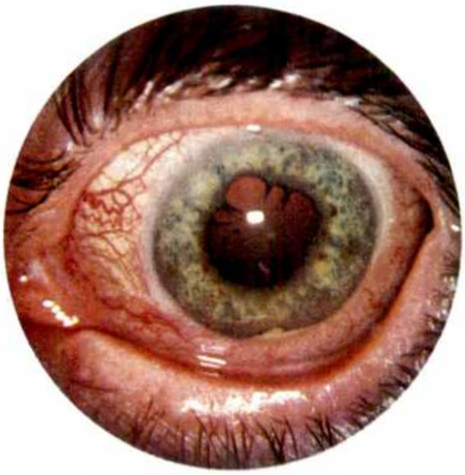

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Keratoconus and coexisting atopic disease

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SUMMARY The association of keratoconus and atopic disease has been reported on several occasions but the only controlled clinical study that has so far been published found no evidence to support this view. Since it is now known that atopy is often associated with changes in various immunoglobulins, particularly IgE, it was considered desirable to determine the immunological profiles of a large series of keratoconus cases in order to seek evidence for coexistence of the two conditions in one individual. In this study of 182 cases of keratoconus a definite history of atopy was found in 35% compared with 12% in the matched control group. The serum IgE was significantly raised ($P<0.001$) in keratoconus and markedly so in those cases with associated atopic disease. Serum levels of IgG and IgM were also raised, but contrary to the findings of other observers IgA levels were normal. These findings suggest that atopic traits are more common in patients with keratoconus than in general ophthalmic patients.

Keratoconus (conical cornea) is a progressive non-inflammatory condition characterised by thinning, ectasis, and eventual scarring of the central cornea. Because of the resulting irregular astigmatism there is a marked loss of vision, which for a while can be corrected by contact lenses, but in most cases corneal transplantation is ultimately required. The disease usually becomes manifest during adolescence, and although it has been known from the earliest times its precise aetiology remains obscure.

An association between keratoconus and atopic disease has been reported in a number of uncontrolled studies (Hilgartner *et al.*, 1937, Galin and Berger, 1958; Spencer and Fisher, 1959; Ridley, 1956), the most recent recording the presence of eczema in 32% of keratoconus patients compared with an assumed incidence of 3% in the general population (Copeman, 1965; Longmore, 1970). Lowell and Carroll (1970), however, failed to detect in their small series of 31 cases any significant difference between the incidence of atopic traits in keratoconus cases and a similar number of unmatched controls when both groups were assessed on the basis of a detailed history and skin tests with common allergens. In spite of this conflicting evidence it has remained our firm clinical impression that atopic traits are more commonly associated with this disease than with other eye conditions. Since it is now known that atopy is often associated with raised levels of IgE together with changes in other immunoglobulins (Taylor *et al.*, 1973) it was considered desirable to study the immunological profile of a large series of keratoconus patients in order to determine the incidence of atopic traits, and in particular to discover whether immunological confirmation of our clinical impressions could be obtained. The present study was undertaken 3 years ago and a preliminary report has already been published (Davies *et al.*, 1976).

Materials and methods

One hundred and eighty-two cases of keratoconus, consisting of 129 males and 53 females were randomly selected from the Contact Lens Department at the High Holborn branch of Moorfields Eye Hospital and assessed for their corneal condition. The general incidence of an atopic state was assessed in only 100 patients, who were also skin-tested when possible. Tears and blood samples were collected from each patient and tested for the following immunological parameters.

The immunoglobulins G, A, M, and D were estimated by radial immunodiffusion techniques using ICL plates. WHO standard sera were used to obtain the reference curve. Because of a skewed distribution the individual values were logarithmically transformed to obtain a Gaussian distribution.

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Immunofluorescence tests were performed on composite block frozen sections consisting of liver, kidney, stomach, oesophagus, and parotid from a rat and the stomach of a mouse. The autoantibodies especially looked for were those against cell nuclei and nucleoli, smooth muscle proteins, reticulin, gastric parietal cells, mitochondria, and microsomes. Rat eye sections were examined for anti-ocular antibodies.

Haemagglutination tests using commercial kits were performed to detect antibodies to thyroglobulin and thyroid microsomal antigens and IgM rheumatoid factor.

IgE in serum and tears was measured by solid-phase radioimmunoassay using a Pharmacia commercial kit.

One hundred age and sex-matched patients who were suffering from non-inflammatory eye disease at the time of examination and were attending eye clinics at Moorfields Eye Hospital were examined for the presence of atopy and questioned about any past history of hay fever, asthma, allergic dermatitis, urticaria, and vernal catarrh. A baseline was thus obtained for the general incidence of atopy in ophthalmic patients.

Student's *t* distribution was applied to test the significance of the differences of the mean values for IgG, IgA, IgM, and IgE in the control population and in the patients with keratoconus. The incidence of atopy and the percentage of the individuals showing IgE levels ≥200 IU/ml were statistically analysed by the chi-square test.

Results

Incidence of atopy: 35% of the keratoconus cases showed atopic tendencies (Table 1) as opposed to the control group, where the incidence was only 12% ($P < 0{\cdot}001$). The atopic individuals in the keratoconus series showed a male:female ratio of 2:1; the commonest allergic disorder was hay fever followed by asthma and eczema. No case of vernal catarrh was seen in the present series.

The serum IgE was generally raised in keratoconus ($P < 0{\cdot}001$) but the levels were much higher in the atopic group than in the non-atopic group. The statistical analyses of these levels are shown in Tables 2 and 3.

The geometric mean levels of immunoglobulins G and M were also raised ($P < 0{\cdot}001$), but IgA levels were not significantly different from those in the control group (Table 4).

Some of these patients showed the presence of a variety of autoantibodies in their sera. But the incidence of antinuclear antibodies (14%), rheumatoid factor (9%), and antibodies to smooth muscle proteins (20%), reticulin (1%), gastric parietal cells (2%) was not significantly different from the control population (Rahi *et al.*, 1976).

There was no significant difference between the

Table 1 *Incidence of atopic disease in keratoconus*

Atopic disease	*Control population (%)*	*Keratoconus (%)*
Asthma	1	3
Eczema	3	2
Hay fever	8	15
Asthma + hay fever	0	7
Eczema + hay fever	0	3
Asthma + eczema + hay fever	0	5
Total	12	35

$\chi^2 = 14{\cdot}7$, $P < 0{\cdot}001$

Table 2 *Immunoglobin E in keratoconus*

Serum level	*Control population (100)*	*Keratoconus (182)*
Geometric mean (IU/ml)	52	205 ($P < 0{\cdot}001$)
Range (IU/ml)	10–272	10–4000

Table 3 *IgE in keratoconus*

Serum level	*Control population (100)*	*Keratoconus, atopic (35)*	*Keratoconus, non-atopic (65)*	*Keratoconus, total (100)*
<200 IU/ml	94%	14 (40%)	39 (60%)	53%
≥200 IU/ml	6%	*21 (60%)	*26 (40%)	*47%

*$P < 0{\cdot}001$

Table 4 *Immunoglobulins in keratoconus*

Serum level		*Control population (100)*	*Keratoconus (182)*	*Significance*
IgG (IU/ml)	Geometric mean	121	140	$P < 0{\cdot}001$
	Range	68–217	71–262	
IgA (IU/ml)	Geometric mean	125	123	Not significant
	Range	55–286	63–460	
IgM (IU/ml)	Geometric mean	151	195	$P < 0{\cdot}001$
	Range	68–333	60–538	

IgE levels in the tears of the control and the keratoconus groups.

Discussion

The clinical impression that keratoconus for some unexplained reason shows a strong tendency to coexist with atopic disorders is confirmed by the high incidence of atopy in this large series. The simple electrophoretic study of Manfredi and Romei (1966), which showed raised gamma globulins in keratoconus, was confirmed in the more recent study of 23 cases of keratoconus by Easty *et al.* (1975), who also found that some of these cases had high levels of IgG, IgM, and IgE. Our present study on a much larger group confirms these findings. In addition it detected a variety of autoantibodies in these cases which have not been reported previously, though admittedly their significance is obscure.

Contrary to the findings of Easty and his associates we did not find any statistically significant difference between the levels of serum IgA in keratoconus and those in the control group. Since Easty *et al.* (1975) did not cite their values it is difficult to make any meaningful comparison or to offer any explanation. Although Kaufman and Hobbs (1970) have documented the possible association of high levels of IgE with low IgA levels in atopic adults, this has been questioned by Taylor *et al.* (1973), who showed that, although atopy and raised levels of IgE may be linked with low IgA levels in blood and body secretions, this is true only for the early months of infancy, when the foundations of many allergic traits are being laid down. This transient IgA deficiency is soon replaced by a normal pattern, and in some individuals the IgA concentration may later rise above the normal range. Our findings are in agreement with these workers and indicate that IgA levels are not significantly low in keratoconus despite high levels of IgE, but this does not of course exclude a transient IgA deficiency during infancy.

The significance of these immunological changes in the natural history of keratoconus is uncertain, since the disease is non-inflammatory and it is difficult to see how immunopathological processes can produce changes in the cornea without inducing any inflammatory reaction. It is known, however, that autoimmune gastric atrophy can be produced in experimental animals (Porteous *et al.*, 1974) without any marked inflammatory response, and the kidney in systemic lupus erythematous may not show any cellular infiltration, though these conditions are the exception rather than the rule in immunopathological disorders.

For some unknown reasons keratoconus seems to coexist with these immunological abnormalities of a generalised type. Ataxia telangiectasia, with vascular changes in the conjunctiva, the Wiskott-Aldrich syndrome with atopic dermatitis involving the eyelids, and short-limbed dwarfism are all syndromes associated with gross immunological abnormalities. No unifying hypothesis has been produced to explain these remarkable combinations of features, nor is it easy at present to explain the observed immunological changes in keratoconus.

It is possible that keratoconus is a *forme fruste* of a functionally abnormal mesenchymal system, manifesting itself only in the eye, and biochemical and ultrastructural studies seem to support this notion. Keratocytes, which are involved in the synthesis and secretion of collagen and proteoglycans (i.e., the ground substance), which exert molecular constraints on the regular organisation of the corneal lamellae (Borcherding *et al.*, 1975), appear to function erratically in keratoconus. The keratocytes show features of active synthesis as well as gradual degeneration and vacuolation (Pouliquen *et al.*, 1972). The synthesis of collagen takes place in various steps involving translation, hydroxylation, helix formation, glycosylation, secretion, conversion of the precursor, aggregation, and cross-linking. These processes are not only dependent on various enzymes, which are genetically controlled, but on several other factors in the micro-environment which may affect the process of cross-linkage and laying down of the collagen in a regular pattern. A defect in any of these processes will affect fibrillogenesis in the cornea and may lead to the changes so commonly seen in keratoconus.

A close relationship exists between atopy, raised IgE, and several histocompatibility antigens, particularly HLA–B7 and haplotypes A1:B8 and A3:B7 (Goodfriend *et al.*, 1973; Turner *et al.*, 1977). Studies on serum levels of IgE in monozygotic and dizygotic twins suggest an inherited genetic function in IgE production (Hamburger and Bazaral, 1972). It would be interesting to investigate a large number of keratoconus cases to see if this disease (like acute anterior uveitis, in which HAL–B27 predominates) shows a preferential clustering around any particular histocompatibility antigen.

Our thanks are due to Professor Norman Ashton, FRS for his kind advice and valuable comments, to Mr J. Prasad and Miss J. Hodges for their technical assistance, and to Mrs A. Wood for secretarial help.

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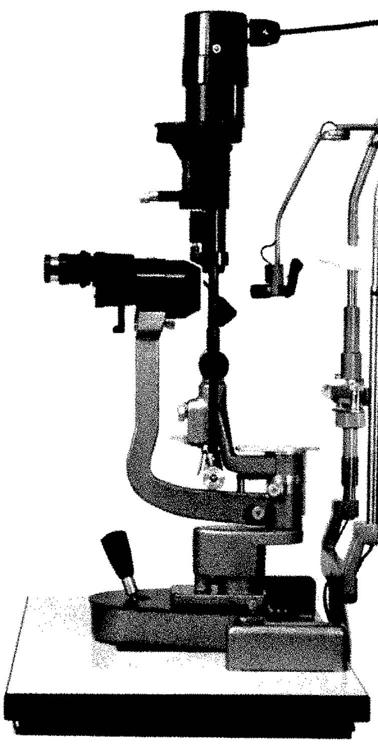

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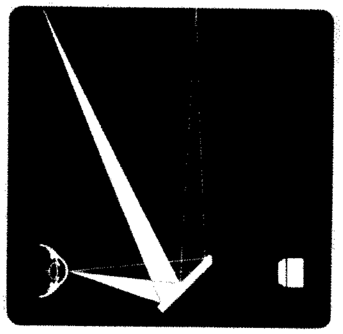

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British Journal of Ophthalmology, 1977, **61**, 765–766

Bilateral cataract: extraction in classic haemophilia with retrobulbar anaesthesia and peripheral iridectomy

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SUMMARY A 47-year-old factor VIII deficient haemophiliac successfully underwent bilateral cataract extraction. The use of cryoprecipitates to achieve haemostasis permitted retrobulbar anaesthesia and a peripheral iridectomy without complication. We consider that the use of cryoprecipitated factor VIII concentrate allows safe elective ocular surgery in patients with classic haemophilia.

The danger of haemorrhage in patients with haemophilia has necessitated postponement of elective ocular surgery or the use of special techniques to avoid untoward bleeding. The advent of cryoprecipitated factor VIII concentrate prepared from human plasma has made possible the restoration of normal haemostasis for the entire operative period. Elective ocular surgery can then be performed with the usual techniques. We wish to describe a patient with classic haemophilia who underwent bilateral cataract surgery by means of retrobulbar anaesthesia and peripheral iridectomies, a procedure not previously described in these patients.

Case report

A 47-year-old male watchmaker was a known haemophiliac since childhood. He had noted steadily decreasing vision in both eyes for the past year. On admission he had visual acuity of hand movements only in both eyes, with normal light projection, 2-point discrimination, and colour perception. Mature cataracts in both eyes prevented fundus examination. Intraocular pressures were normal.

General physical examination was normal. Laboratory findings are shown in Table 1. No evidence of a circulating inhibitor of factor VIII activity was found.

One hour before operation 1600 units of factor VIII concentrate was intravenously infused. Surgery was performed in the right eye by means of retrobulbar anaesthesia and Atkinson facial nerve block. A superior rectus suture was placed. An incision was made in clear cornea followed by a peripheral iridectomy. Cryoextraction of the lens was performed after the use of chymotrypsin. The corneal wound was closed with interrupted 8·0 silk sutures. No unusual bleeding was noted during the entire operative period. Postoperatively the patient continued to receive 800 units of factor VIII concentrate every 12 hours for 7 days. No haemorrhages were seen in the postoperative period. The patient was discharged 12 days after surgery.

At examination 10 weeks later the patient had 6/9 vision with his aphakic correction, but complained of difficulty working as a watchmaker because of the absence of binocular vision. He therefore was readmitted for cataract extraction in his left eye.

Preoperatively the factor VIII level was now found to be 7·5%. The other pertinent tests were not significantly different from those shown in Table 1.

Table 1 *Results of coagulation tests in our patient*

Coagulation test	*Patient*	*Normal*	*Control*
Clotting time (Lee and White method)	21 min 5 s	less than 5 min	
Prothrombin consumption	26·8 s		15·0 s
Fibrinogen (mg/100 ml)	380	150–360	
Platelet count	248 000	above 200 000	
Bleeding time (Ivy method)	2 min 30 s	2·5–7 min	
Tourniquet test	negative	negative	
Partial thromboplastin time	53·4 s		34·5 s
Factor VIII assay (Owen method)	10%		

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Preoperative treatment, operative procedure, and postoperative care were as in the first admission. No abnormal bleeding occurred. However, the first day after operation the anterior chamber was found to have 4+ cells and fibrin with a small hypopyon. Because of the possibility of endophthalmitis a subconjunctival injection of gentamicin 40 mg was given. No subconjunctival bleeding at the site of injection was observed. The anterior chamber cleared within 24 hours with conservative treatment with atropine, steroid, and antibiotic drops. The subsequent postoperative recovery was uneventful, and the patient now sees 6/12 with his aphakic correction in the left eye. He is satisfied with his binocular vision and has returned to work.

Discussion

The introduction of cryoprecipitates made it practicable for blood banks to produce factor VIII in concentrated form at a reasonable cost (Pool *et al.*, 1964). The use of this concentrate is now standard in the treatment of classic haemophilia (Dallman and Pool, 1968). Despite this, ophthalmic surgeons continue to use special precautions in cataract extractions in these patients, such as general anaesthesia and omission of iridectomy (Osterlind and Nilsson, 1968; Strauss and Ramsell, 1968; Richards and Spurling, 1973).

Before the introduction of factor VIII concentrates, prolonged bleeding after ocular surgery was a dreaded complication (Rubinstein *et al.*, 1966). The occurrence of a retrobulbar haemorrhage could lead to permanent visual loss (Zimmerman and Merigan, 1960). Surgical procedures were to be avoided if possible (Rubinstein *et al.*, 1966). However, since the introduction of cryoprecipitated factor VIII concentrate the approach to elective general surgery has changed (Cooke *et al.*, 1968). We therefore felt justified in attempting cataract extraction in our patient using our standard operating procedure while replacing his deficient clotting factor in the manner outlined by Richards and Spurling (1973). Our only modification was in the use of a corneal section because of the rare occurrence of a hyphaema even months after surgery due to focal vascularisation of limbal wounds (Swan, 1973). In a haemophiliac such bleeding into the eye would be especially hazardous.

It is worthwhile to note that our patient had what is considered mild haemophilia with factor VIII levels between 7·5% and 10%. These levels uncommonly cause spontaneous bleeding but are associated with severe and unsuspected bleeding at surgery. Levels of factor VIII activity of at least 25% are generally regarded as necessary to prevent surgical complications (Wintrobe, 1974). Because of the good results in our patient we feel encouraged to attempt such an approach in other haemophiliacs who until now were discouraged from undergoing elective ocular surgery. This becomes especially meaningful as the life expectancy of haemophiliacs continues to increase with the availability of effective therapeutic materials.

Our thanks to Dr A. Divilansky for the haematological studies and Mrs Bilha Savell for technical assistance.

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On the relationship between strabismic amblyopia and eccentric fixation

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SUMMARY Landolt C and grating acuity are compared with that normally expected of the eccentric fixation region for 10 strabismic amblyopes. The findings suggest that 2 populations of amblyopes exist. For some amblyopes visual function is that predicted of the eccentric region used for fixation, whereas for other amblyopes there is a further pathological reduction in visual function. These findings may have an important bearing on the type of orthoptic treatment used for amblyopia.

The relationship between the magnitude of the visual abnormality and the degree of eccentric fixation in strabismic amblyopia has been a controversial issue for many years. Although much research has been directed towards understanding this issue, only 2 studies have tackled the problem quantitatively, and they have produced results which seem to be contradictory.

Flom and Weymouth (1961) found a linear relationship between the minimum angle of resolution and the degree of eccentric fixation for 9 amblyopic subjects. Furthermore, the slope of this function (1·79 min of arc/deg of eccentric fixation) corresponded reasonably well with that obtained for normal untrained subjects (1·77 min arc/deg of eccentric fixation) for eccentric viewing. This result led to the conclusion that the decline in acuity for amblyopic eyes could be ascribed to the expected normally low acuity of the eccentric region used for fixation. Contrary to this view, Alpern *et al.* (1967) found that the function relating amblyopic letter acuity and eccentric fixation did not coincide with that describing the acuity loss of the normal peripheral retina. They concluded that in strabismic amblyopia a further pathological loss of acuity is superimposed upon the normally low acuity expected of the eccentric retinal area used for fixation.

This conflict which has developed concerning the relationship between the visual abnormality and the degree of eccentric fixation in amblyopia needs to be reassessed, because it has an important bearing on the nature, cause, and treatment of amblyopia and the role of the eccentric fixation in this condition. The present investigation reassesses this problem by comparing letter and grating acuity for centrically and eccentrically fixating amblyopes with that expected of the normal peripheral retina. Grating acuity offers a number of important advantages over letter acuity for this type of investigation. It represents a cognitively, spatially, and orientationally simpler task then letter acuity, and its accuracy is equal for normal and amblyopic eyes (Hess and Howell, in press) and does not vary as a function of eccentric viewing.

Apparatus and methods

ACUITY TESTS

Landolt C acuity.—A frequency-of-seeing curve was constructed from multiple (28) presentations of different sized single Landolt Cs (approximately 100% contrast), and the acuity was taken as the gap size at which $P=0{\cdot}5$. This threshold was determined by probit analysis (Finney, 1947) of the frequency-of-seeing data. No temporal factor was incorporated in the test, although the subjects were asked to respond promptly after the Landolt C was presented. The background luminance was 30cd/m^2, the subjects were optically corrected, and a 3 mm artificial pupil was used. The natural pupil was dilated and accommodation paralysed with 2 drops of 2% homatropine prior to the refraction.

Grating acuity.—Vertical, spatially modulated sine-wave gratings of variable contrast and frequency were generated on the screen of a modified BWD oscilloscope by the method and equipment previously described (Hess and Howell, in press). The space-averaged luminance was 30cd/m^2 and the contrast modulation which occurred about this luminance was adjusted by the subject with an 80-position switched logarithmic attenuator. The oscil-

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loscope screen was masked down to a 7·5 cm circular aperture. A 100 × 75 cm white surround screen was obliquely illuminated to the same luminance (3% difference at aperture edge) and colour ($2\frac{1}{2}$ JNDs on uvw CIE colour system (Wyszecki, 1963). The room illumination was adjusted by means of indirect lighting to approximate to that of the screen and surround. The viewing distance from the oscilloscope was varied from 114 cm for spatial frequencies up to 10 c/deg to 342 cm for higher spatial frequencies. The field size therefore varied from 3·7 to 1·2°. Subjects were located by means of a headrest and all observations were made with a 3-mm diameter artificial pupil, mydriasis, and cycloplegia. Care was taken in the centering of the artificial pupil so that maximum acuity was achieved (Campbell and Gregory, 1960). Two drops of 2% homatropine were instilled in each eye prior to the refraction. A careful clinical refraction was performed with the artificial pupils in place, and then the subject's prescription was modified for the testing distances used.

The method of adjustment was used in determining contrast thresholds. Instructions and training were standardised for all subjects to minimise threshold criterion changes and so to facilitate intersubject comparisons. The experimental protocol was such that contrast sensitivity for each spatial frequency was measured for the normal and amblyopic eye alternately. This design allows a more valid intrasubject comparison between normal and amblyopic curves. Five readings were taken at each spatial frequency tested.

Sine-wave grating acuity was estimated by extrapolation of the high frequency contrast sensitivity results. The high frequency sine-wave contrast sensitivity results were fitted by linear regression on semilog co-ordinates (Campbell *et al.*, 1966) and then extrapolated to the abscissa. This technique was adopted because it was impossible to generate 100% contrast stimuli on a video display. The frequency response and contrast linearity of the video monitor were checked with a PIN photo diode.

ECCENTRIC FIXATION MEASUREMENT

A battery of tests were used to assess the fixation pattern of the amblyopic and normal eyes tested. These were: (1) Maxwell's spot; (2) Haidinger's brushes; (3) visuscopy; and (4) fixation photography. None of these tests are satisfactory alone for reasons which will be discussed; however, the combined result of all the tests gives a greater degree of confidence concerning the degree of eccentric fixation.

Maxwell's spot.—The subject viewed a retro-illuminated bull's eye target which was located 282 cm away (rings ranged from $\frac{1}{2}$° diameter to 4° diameter in $\frac{1}{2}$° steps) through alternating purple (Kodak Wrattan No 34) and neutral filters. The two filters were matched for transmittance with a Spectra Pritchard spot photometer for the viewing conditions of the test. The subject adjusted the speed of alternation (for any desired mark space ratio) and the target illumination for optimum viewing of the entoptic spot. The most common alternation frequency (0·5 mark space ratio) and target illumination was 0·5 to 1 alternation/s and 4 cd/m^2 respectively. The subjects were first shown the spot with their good eye and asked to arrange optimum viewing conditions. They were asked to describe and sketch the shape and size of the spot and estimate its centre with respect to the fixation target. Three estimations were recorded, and the procedure was repeated for the amblyopic eye. Although there was considerable variation in the reported shape and size of the spot, the 30 min central dark disc was always seen (except for Case 7, who did not perceive the spot at all), and its centre was taken as an estimate of fixation.

Haidinger's brushes. The subject viewed a retro-illuminated bull's eye target (similar to that already described for the Maxwell spot test) through a blue filter (Kodak Wrattan No. 50) and rotating Polaroid (HN-22) filter. The subject adjusted the speed of rotation of the Polaroid filter and the target luminance for optimum viewing of Haidinger's brushes. The most commonly selected speed of rotation and target luminance through the filters was 60–300 RPM and 60 cd/m^2 respectively. The same procedure was adopted as for the previous test; three determinations of the pivot point of the rotating brushes were first made for the normal and then for the amblyopic eye. The angular size of the brushes was typically 1°, and, although in some cases the central region was not seen, the point about which the outer structure appeared to rotate could be accurately estimated with respect to the fixation centre.

Visuscopy and fixation photography. The Keeler specialist visuscope/euthyscope set was used in this investigation. For fixation photography a Topcon retinal camera (model TRC-J) was especially modified for this task by the inclusion of a target (photographically reduced target on a 35 mm slide), which could be introduced into the illumination system, at the point conjugate with the retina for an emmetropic eye. At another location in the illumination system lenses could be inserted to focus correctly the fixation target for myopic, presbyopic, or highly hyperopic subjects. Twenty photographs were taken for each subject of the fixation relationship for the normal and amblyopic eye. The fundus slides were

Table 1 *Eccentric fixation measurements for the 10 strabismic amblyopes tested*

	Amblyopic eyes				
Case	*Maxwell's spot*	*Haidinger's brushes*	*Visuscope*	*Fixation photography*	*Mean (retina)*
1	Right eye 13·2′ ± 4·3′ (Nasal)	28′ ± 4′ (Nasal)	1° ± 30′ (Nasal)	1·8° ± 30′ (Nasal)	52·3′ (Nasal)
2	Right eye 8·5′ ± 12′ (Temporal)	7·9′ ± 2′ (Temporal)	Central	Central	4·1′ (Central temporal)
3	Left eye 1·7° ± 7′ (Temporal)	1·4° ± 20′ (Temporal)	No reflex	2·8° (Temporal)	1·96° (Temporal)
4	Left eye 2·6° ± 20′ (Inferior temporal)	2·2° ± 10′ (Inferior temporal)	No reflex	3° (Inferior temporal)	2·6° (Inferior temporal)
5	Left eye 2·7° ± 15′ (Nasal)	3·1° ± 10′ (Nasal)	No reflex	3·2° (Nasal)	3° (Nasal)
6	Left eye 1·8° ± 20′ (Nasal)	2° ± 20′ (Nasal)	1·5° ± 30′ (Nasal)	1·4° ± 30′ (Nasal)	1·3° (Nasal)
7	Left eye Not seen	2·1° ± 15′ (Temporal)	3° ± 30′ (Temporal)	2·5° ± 30′ (Temporal)	2·5° (Temporal)
8	Right eye 2·0° ± 18′ (Nasal)	2·1° ± 17′ (Nasal)	1·5° ± 30′ (Nasal)	1·6° ± 30′ (Nasal)	1·8° (Nasal)
9	Right eye Central	Central	Central	Central	Central
10	Right eye Central	Central	Central	Central	Central

Normal eyes: Maxwell's spot: Normal variation 7′–14′. Haidinger's brushes: Normal variation 2·6–12′

projected and the target position (dimensions: outer ring 2° in diameter, inner fixation spot 30 minutes diameter) was assessed relative to foveal landmarks. The distance from the fovea to the optic disc centre was measured and taken to be 17° (Van Buren, 1963). The results of these 4 tests for eccentric fixation are summarised in Table 1.

SUBJECTS

With one exception (Case 4, high anisometropia) only subjects who satisfied the following requirements were selected. These requirements were: (1) no high unilateral or bilateral astigmatism; (2) no high anisometropia; (3) a normal fixing eye (i.e., visual acuity correctable to at least 6/6 and no signs of ocular disease); (4) strabismus; (5) full orthoptic treatment and/or strabismic amblyopia history available from the departmental clinic; (6) reliable observer; and (7) no other ocular abnormality present. These requirements ensured that only strabismic amblyopia was studied and that there were no confounding influences from spherical ametropic amblyopias, meridional amblyopia, or other ocular abnormalities which may be associated with a strabismus. The clinical data for these strabismic amblyope representatives are summarised in Table 2.

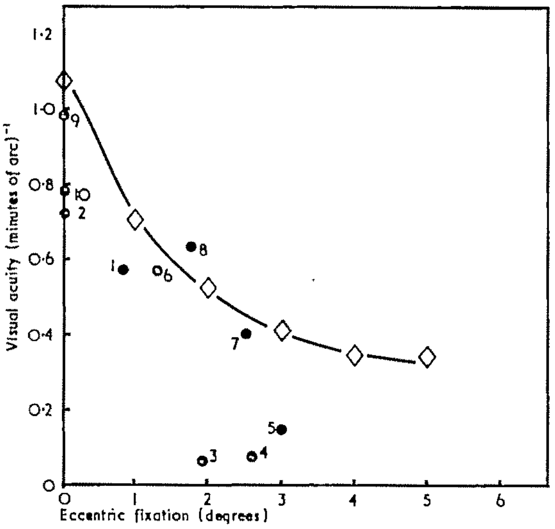
Results

Table 1 shows the degree of eccentric fixation recorded from the 4 tests used, the average of which was taken as the best estimate and appears in Table 2. For 3 patients visuscopy was useless, as no foveolar reflex was present, and for 1 patient Maxwell's spot was not seen with her amblyopic eye. There may be grounds for thinking that visuscopy and fixation photography might produce greater degrees of eccentric fixation, perhaps as an artefact of their very high luminances, as it has been reported that the fixation eye movements in the amblyopic eye increase in amplitude in very bright light (Von Noorden and Burian, 1958; Lawwill, 1966). In only 5 of the patients was the degree of eccentric fixation greater for these high luminance tests and for 3 out of the 5 this difference was less than ½°, which is the

Table 2 *Conventional clinical data for the 10 strabismic subjects*

Case	*Sex, Age (yrs)*	*Cycloplegic refraction (3 mm art. pupil)*	*Snellen chart acuity (30 cd/m²)*	*Psychometric Landolt C. acuity (30 cd/m²)*	*Monocular fixation (deg)*	*Angle and type of deviation (6 m photography deg)*	*Age first noticed*	*Details of amblyopia/strabismic therapy*
High frequency only loss class								
2	F 22	R $\frac{+0{\cdot}75\text{D}}{-0{\cdot}75}$ ×20	R 6/9	R 6/8·3	R Central	2 R Exotropia	9 years	Decreased vision in right eye detected at age 9. R_x worn until age 12. Squint detected at age 16. No therapy undertaken
		L $\frac{+0{\cdot}50\text{D}}{-0{\cdot}50}$ ×20	L 6/5	L 6/6	L Central			
8	F 18	R −1·25D	R 6/21	R 6/8·9	R 1·8°	4 R Esotropia	5 years	Total direct occlusion at age 5½ years for two 6-week periods. Therapy discontinued at age 6 years
		L $\frac{-1{\cdot}00\text{D}}{-0{\cdot}50}$ ×70	L 6/5	L 6/5·4	L Central			
6	F 17	R +1·00D	R 6/7·5	R 6/6·4	R Central	3 L Esotropia	3 years	Total direct occlusion at age 3 years for 1 year followed by R_x worn with one frosted lens for 2 years. Only small improvement resulted. R_x worn intermittently, orthoptics for 1 year at age 16
		L +3·50D	L 6/15	L 6/10·4	L 1·3°			
9	F 35	R $\frac{+0{\cdot}75\text{D}}{-0{\cdot}50}$ ×25	R 6/9	R 6/6·1	R Central	6 R Exotropia	6 years	R_x worn intermittently from 6 years to 13 years. No orthoptics
		L $\frac{+0{\cdot}75\text{D}}{-0{\cdot}50}$ ×140	L 6/4·5	L 6/4·6	L Central			
1	M 25	R $\frac{+0{\cdot}25\text{D}}{-0{\cdot}25}$ ×105	R 6/21	R 6/10·1	R 0·86°	4 R Esotropia	7 years	At age 7 fusional exercises and total direct occlusion for 2 years. Therapy discontinued at age 12 years—some success achieved
		L $\frac{+0{\cdot}50\text{D}}{-0{\cdot}75}$ ×30	L 6/6	L 6/6·4	L Central			
Low and high frequency loss class								
7	F 24	R +0·75D	R 6/4·5	R 6/4·5	R Central	3 L Exotropia	18 months	Large esotropia—total direct occlusion at age 2 years for 6 months—unsuccessful. Squint operation age 5 years followed by total occlusion: R_x worn intermittently from 5 to 16 years
		L $\frac{+0{\cdot}75\text{D}}{-0{\cdot}25}$ ×140	L 6/30	L 6/15·5	L 2·5°	3 L Hypertropia		
4	F 23	R $\frac{-6{\cdot}00\text{D}}{-1{\cdot}50}$ ×155	R 6/5	R 6/6·6	R Central	11 L Exotropia	7 years	At age 7 complained of unilateral blur. Age 11 years squint operation—cosmetic success only. No other undertaken
		L −19·00D	L 6/90	L 6/76·2	L 2·6°			
10	F 23	R $\frac{+0{\cdot}25\text{D}}{-0{\cdot}50}$ ×20	R 6/15	R 6/7·5	R Central	4 R Exotropia	3 years	Total direct occlusion at age 3 for 6 to 8 months—some success. At age 10, 5° esotropia with R 6/15. Orthoptics until age 12—minimal success
		L $\frac{\text{plano}}{-0{\cdot}50}$ ×100	L 6/4·5	L 6/4·3	L Central			
5	F 23	R $\frac{+4{\cdot}75\text{D}}{-0{\cdot}75}$ ×115	R 6/5	R 6/4·4	R Central	21 L Esotropia	9 months	Squint operation at age 1 year. R_x worn for 4 years. Total direct occlusion at age 8 for 3 weeks followed by orthoptics for 6 months—minimal success
		L $\frac{+6{\cdot}50\text{D}}{-1{\cdot}50}$ ×170	L 6/84	L 6/39·9	L 3°			
3	F 24	R $\frac{+2{\cdot}50\text{D}}{-0{\cdot}50}$ ×40	R 6/5	R 6/4·1	R Central	5 L Exotropia	3 years	Amblyopia first detected at age 3 years. No therapy or R_x. First R_x at age 10 years, worn intermittently. No strabismus detected
		L +2·75D	L 6/90	L 6/76·9	L 2°			

*All subjects tested had normal pursuit eye movements, normal fundus oculi, constant strabismus and harmonious abnormal retinal correspondence



accuracy estimate of these tests. The range of variation for the normal eyes for Maxwell's spot and Haidinger's brushes was 7 to 14′ and 2·6 to 12′ respectively. The normal eyes' range of variation for visuscopy and fixation photography was within 20 min of the fovea. The degree of eccentric fixation in all except Case 7 was less than the angle of strabismus, an observation which agrees with previous investigations (Von Noorden, 1970a, b).

Fig. 1 shows a comparison between the results of Millodot (1966) for normal letter acuity (single Landolt C acuity for 3 subjects using an identical

Fig. 1 *The relationship between single Landolt C psychometric acuity for centrally and eccentrically fixating amblyopes* (filled symbols) *and the normal Landolt C acuity of the peripheral retina* (open symbols). *Case numbers shown against dots*

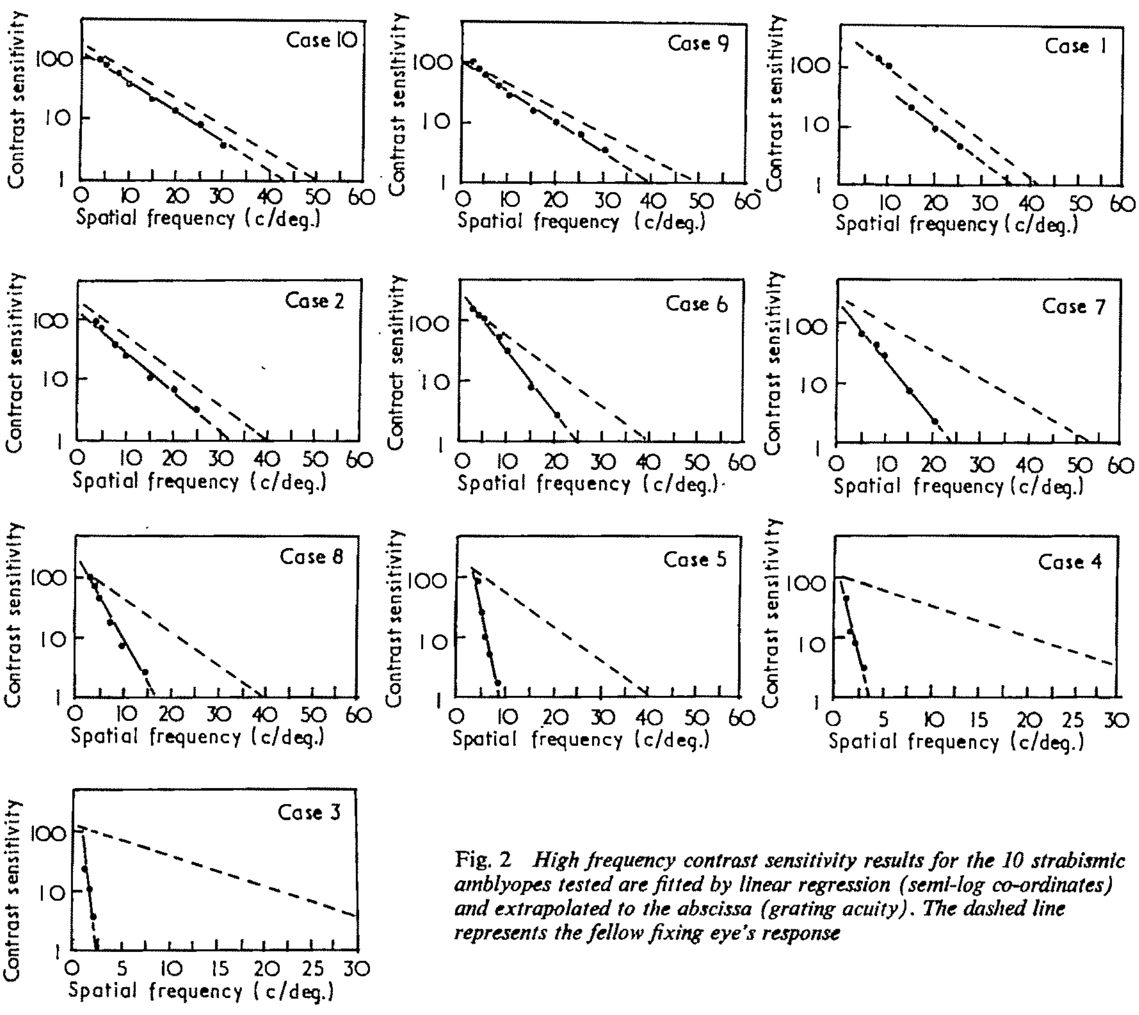


Fig. 2 *High frequency contrast sensitivity results for the 10 strabismic amblyopes tested are fitted by linear regression (semi-log co-ordinates) and extrapolated to the abscissa (grating acuity). The dashed line represents the fellow fixing eye's response*

psychometric technique) versus eccentric fixation and the Landolt C, 50% thresholds of the 10 strabismic amblyopes in the present investigation. No luminance correction is necessary for these normal results, as the luminance difference is slight and is on the plateau, where letter acuity is relatively independent of luminance (Schlear, 1937). These results indicate that, although the correlation coefficient between Landolt C acuity and eccentric fixation was 0·62 ($0{\cdot}05 > P > 0{\cdot}01$) for the amblyopic eyes, only 3 of the 10 amblyopes (Cases 6, 7, 8) showed acuities which were consistent with that expected from the eccentric retinal region used for fixation.

The individual high frequency contrast sensitivity results (SE of mean is equivalent to symbol size) for the 10 strabismic amblyopes from which the grating acuity results were derived (extrapolation to abscissa) are displayed in Fig. 2. In all cases these contrast sensitivity results have been fitted by linear regression; the correlation coefficient was not less than 0·969, and this corresponded to a significance level less than 0·01. Fig. 3 incorporates these derived amblyopic grating acuities versus eccentric fixation, and this is compared with the normal grating acuity expected of the peripheral retina. The normal grating acuity of the peripheral retina was measured using the same equipment, experimental technique, and conditions for subject ERH. These normal results (displayed in the inset of Fig. 3) are for a ¼° field size for frequencies greater than 5 c/deg and 1° field-size for 5 c/deg. Care was taken to ensure minimal interference from the 'edge effect', which can invalidate high frequency measurements for a small field size (Campbell *et al.*, 1969). The results indicate that although the correlation co-efficient was 0·85 ($0{\cdot}01 > P > 0{\cdot}001$) between grating acuity and eccentric fixation for the amblyopic eyes, only 2 out of 10 amblyopes (Cases 1, 7) had grating acuities which can be explained solely on the basis of the expected acuity of the eccentric region of fixation.

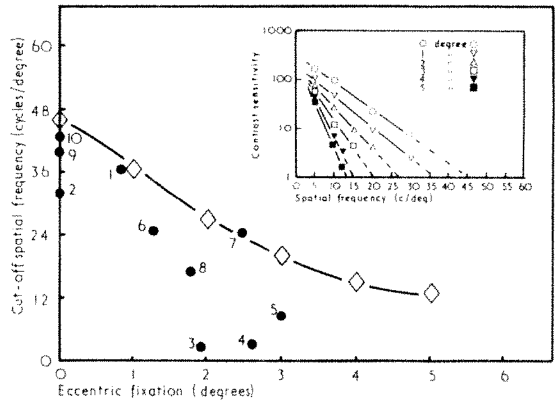


Fig. 3 *The relationship between grating acuity for centrically and eccentrically fixating amblyopes* (filled symbols) *and the normal grating acuity of the peripheral retina* (open symbols). *The normal grating acuity versus eccentric viewing was derived from the extrapolation of the data in the figure inset. Case numbers shown against dots*

Discussion

The results from both acuity tests indicate that 2 populations of strabismic amblyopes can be differentiated when their acuity (letter or grating acuity) is compared with that expected from the eccentric region used for fixation. Acuity for one group of amblyopes can be totally explained by the normally low acuity expected from the peripheral retinal region used for fixation. For a second group of amblyopes there is a further pathological reduction in acuity beyond that expected of the eccentric fixation region. The spatial frequency extent of this depression is yet to be determined. These results explain why the previous two studies (Flom and Weymouth, 1961; Alpern *et al.*, 1967) have produced contradictory results.

It is interesting that there was not absolute agreement between the two acuity tests as to which amblyopes have acuity expected from the eccentric region used for fixation. For example, only Case 7 gave a consistent result for the 2 acuity tests. This may indicate that more than high frequency discrimination is important for Landolt C detection and that, at least for threshold tasks, an overall frequency depression may be less visually debilitating for detection of complex targets than a differential frequency depression (Bodis-Woolner, 1972).

The conclusion that some amblyopes' visual function is predictable on the basis of the normally low acuity of the eccentric area of fixation is supported not only for grating acuity but also for contrast sensitivity measurements at spatial frequencies within the resolution limit. This finding is clearly seen in Figs. 4 and 5, in which the contrast sensitivity results for Cases 1 and 7 are compared with the sensitivity expected of the normal peripheral retina (ERH results from Fig. 2 inset). Case 1, who has 52′ eccentric fixation, shows high frequency (> 10c/deg) contrast sensitivity, which matches that expected from 1° eccentric viewing (Fig. 4). Case 7, who has 2·5° eccentric fixation, shows high and medium frequency contrast sensitivity, which falls within that expected from between 2 and 3° eccentric viewing (Fig. 5). These results do not support a primary motor basis of amblyopia, because it has previously

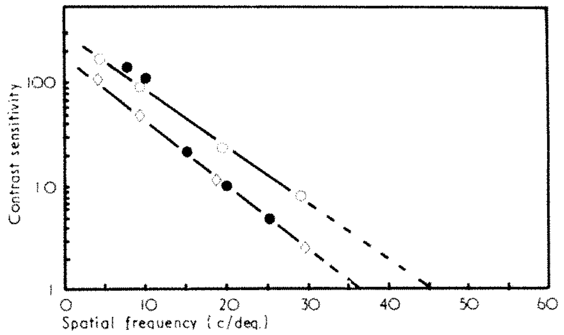


Fig. 4 *The high frequency contrast sensitivity results for case 1* (filled symbols) *are compared with the sensitivity expected on the basis of the eccentric fixation present* (unfilled symbols)

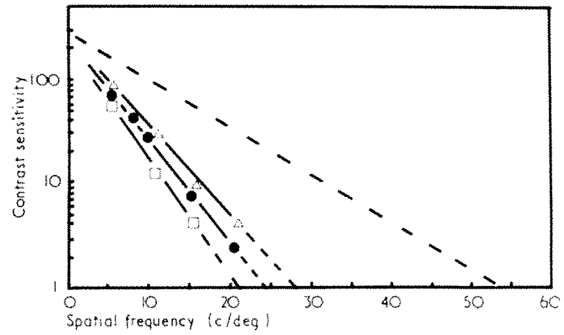


Fig. 5 *The high frequency contrast sensitivity results for case 7* (filled symbols) *are compared with the sensitivity expected on the basis of the eccentric fixation present* (unfilled symbols)

been shown (Hess, in press) that for these two amblyopes the foveal high frequency response is not superior to that of the eccentric fixation region.

The findings of this present investigation may be of interest to clinicians who are concerned with the treatment of amblyopia. Improvement of visual function for some amblyopes will necessitate a reduction in the degree of eccentric fixation, whereas for other amblyopes visual improvement may not necessarily require a change in the fixation behaviour. If the small sample of amblyopes used in the present investigation is representative, this latter response may be more common.

I thank Mr E. R. Howell for acting as a subject for these experiments and for the use of equipment. I would also like to acknowledge the generosity of all my amblyopic subjects.

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Gaze failure, drifting eye movements, and centripetal nystagmus in cerebellar disease

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SUMMARY Three abnormalities of eye movement in man are described which are indicative of cerebellar system disorder, namely, centripetally beating nystagmus, failure to maintain lateral gaze either in darkness or with eye closure, and slow drifting movements of the eyes in the absence of fixation. Similar eye movement signs follow cerebellectomy in the primate and the cat. These abnormalities of eye movement, together with other signs of cerebellar disease, such as rebound, alternating, and gaze paretic nystagmus, are explained by the hypothesis that the cerebellum helps to maintain lateral gaze and that brain stem mechanisms which monitor gaze position generate compensatory biases in the absence of normal cerebellar function.

Cerebellar disease in man causes a variety of abnormalities of eye movement, including dysmetria (Orzechowski, 1927), gaze paretic nystagmus (Holmes, 1917), and rebound nystagmus (Hood *et al.*, 1973). Examination of the direct-coupled electro-oculographic (EOG) records obtained in the Medical Research Council's Hearing and Balance Unit has revealed three additional abnormalities not previously reported in man which we consider are also indicative of cerebellar system disorder, namely, centripetal nystagmus, in which the fast phase of the nystagmus beats towards the position of primary gaze, failure of gaze maintenance after eye closure or in darkness, and drifting movements of the eyes in the absence of fixation.

Methods

PATIENTS

All patients with centripetal nystagmus were surveyed. It was found that centripetal nystagmus occurred in patients with peripheral vestibular lesions, those intoxicated with drugs or suffering from congenital abnormalities, and in patients with disorders of the central nervous system. The characteristics of nystagmus in peripheral lesions are well documented and are discussed later. Drug-intoxicated and congenitally abnormal patients were excluded from the study because of the inability to specify the lesions in these cases. The remaining 17 patients, ranging in age from 23 to 73 years, had subacute or chronic disorders of the central nervous system. The only clinical feature common to all was evidence of a cerebellar system disorder, although the majority did have a wide variety of signs indicative of involvement of other systems—for example, pyramidal system, cranial nerve palsies. A detailed clinical description of the cases used to illustrate abnormalities of eye movement in this paper is given in the Appendix. Of the 17 cases 5 had a cerebellar tumour, 4 multiple sclerosis, 7 degenerative and vascular disease, and 1 Arnold-Chiari malformation.

The diagnosis of cerebellar tumour was verified at operation in all five cases; one patient had a haemangioblastoma and the remainder had astrocytomas. All the patients with a diagnosis of multiple sclerosis were classified as definite by McAlpine's criteria (McAlpine *et al.*, 1972). Three of these had a history of relapse and remission, while the fourth had the progressive form of the disease. A diagnosis of vascular disease was made in patients who had a history with an acute onset and who had hypertension or other signs of vascular disease. Degenerative disease of the central nervous system was diagnosed in patients with a known family history, progressive neurological disturbance in patients older than 50 years, or if there was radiological evidence of atrophy of the cerebellum. The diagnosis in the patient with Arnold-Chiari malformation was confirmed at operation.

Results

CENTRIPETAL NYSTAGMUS

Centripetally beating nystagmus was present, by

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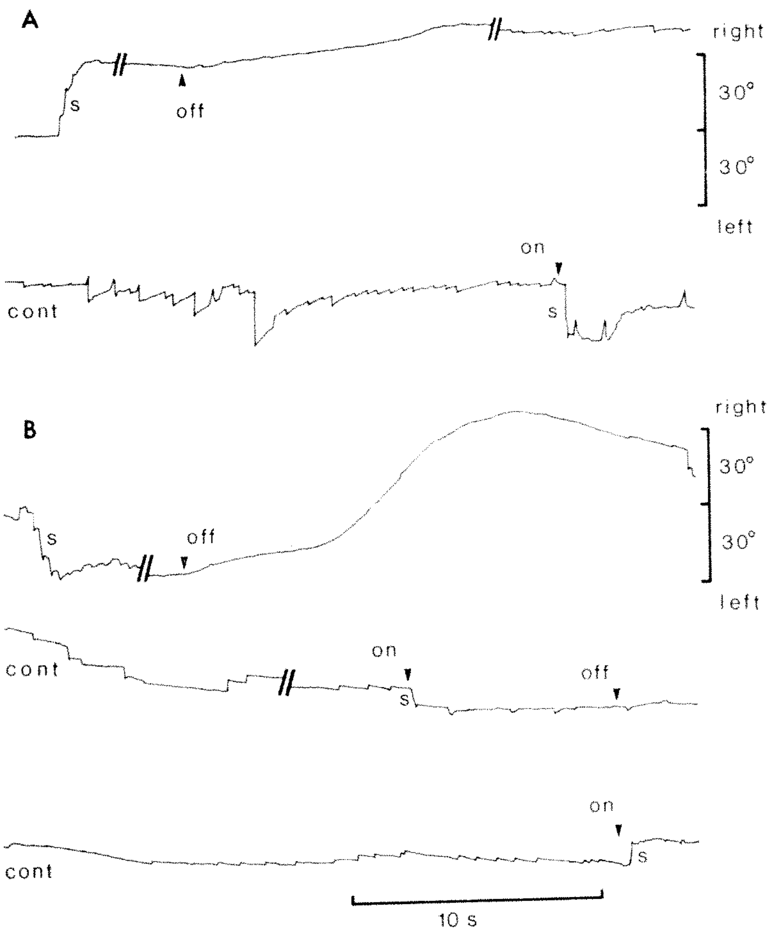

Fig. 1 *EOG recordings of horizontal eye movements in a patient with vascular disease* (case 1).

A. *The patient's eyes are initially in primary gaze, fixated on a central target light in an otherwise dark environment. A second target light appears 30° to the right and the central light is extinguished. The patient executes saccadic eye movement(s),* s, *to fixate the new target. Subsequently the target is turned off for 1 minute, and in total darkness the eyes drift further to the right; small saccadic movements beating to the left begin and attempts are made to correct the drift (*cont *= continuation of the recording). Eventually a distinct nystagmus is evident. The target finally reappears 30° to the right and corrective movements,* s, *are made for refixation.*

B. *The experimental regime is the same as in* A, *but this time the lateral target appears at 30° left. When it is extinguished, the eyes drift to the extreme right and then back to the left with the assistance of small saccades (earliest portion of the first continuation trace). The eyes continue to drift to the left, and right-beating nystagmus develops. The target light is turned on for 4 seconds to correct the position of the eyes,* s, *and a fine left-beating nystagmus is immediately evident. The target is turned off for a further 28 seconds, and in this period of darkness the second continuation trace shows that the eyes drift further to the left and a right-beating nystagmus appears. A final rightward correction,* s, *is made when the target light is turned on again.*

Net EOG drift estimated with reference to eye position during target refixations—1°/minute.

definition, in all patients in the survey. Such nystagmus occurred in the presence of optic fixation, in darkness, or on eye closure. An example of a bilateral centripetal nystagmus occurring in darkness is presented in Fig. 1. When illumination is turned off, the patient's eyes drift about in the darkness and a centripetally beating nystagmus develops. The centripetal nystagmus is immediately abolished when the illumination is turned on again and is replaced by centrifugal nystagmus (Fig. 1B). In some other patients a centripetal nystagmus was seen immediately the eyes attained an eccentric gaze position.

An example of predominantly unilateral centripetal nystagmus following eye closure is presented in Fig. 2B. After closure there is a failure to maintain lateral gaze, and the eyes assume a more neutral position. During the movement towards the neutral position a centripetal nystagmus appears. Fifteen patients had a unilateral centripetal nystagmus, which could occur under conditions of darkness, closure, or fixation, or any combination of these. Of the 2 remaining patients one had bilateral centripetal nystagmus in darkness; the other had a unilateral centripetal nystagmus in one direction in darkness and in the other direction on eye closure.

FAILURE OF GAZE MAINTENANCE

A failure of gaze maintenance means that the eyes move rapidly from an eccentric gaze position towards

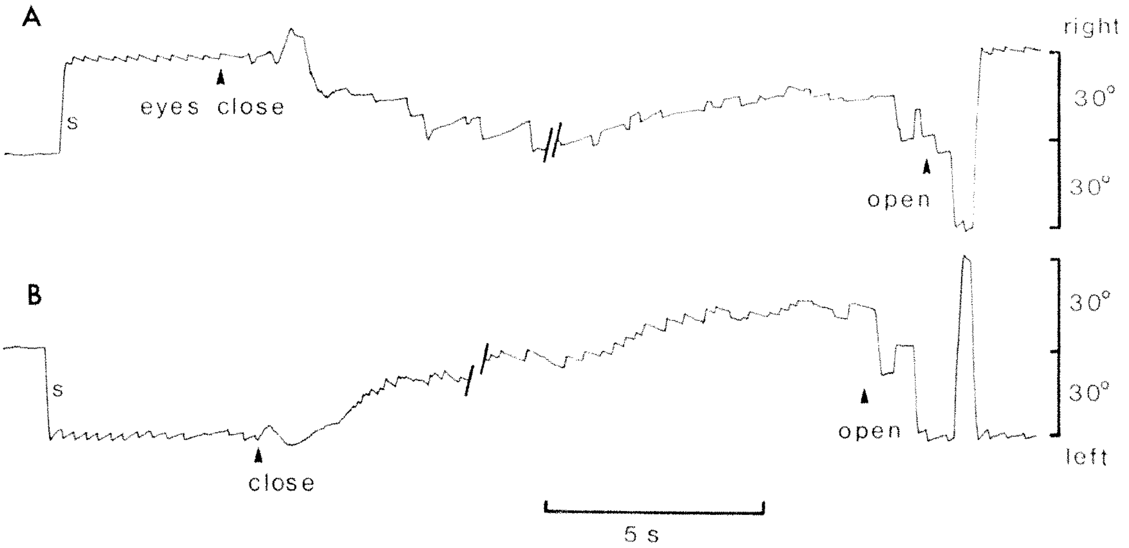

Fig. 2 *EOG recordings of horizontal eye movements in a patient* (case 2) *after surgical removal of a tumour arising from the lateral part of the floor of the fourth ventricle and affecting the left cerebellar hemisphere.*

A. *Initially the eyes fixate a target light in primary gaze. A second target light appears 30° to the right and the patient fixates it,* s. *Immediately a right-beating nystagmus (1°) develops. After eye closure there is a rapid drift towards primary gaze, on which is superimposed a left-beating nystagmus such that the net eye movement is towards primary gaze, but the slow-phase movement is to the right. Eventually the nystagmus ceases and the eyes drift to the right and show small irregular saccadic movements with occasional isolated, nystagmic beats. The eyes open, and after a short series of inappropriate movements the 30° right target is refixated and the right-beating (1°) nystagmus reappears.*

B. *A target 30° left is fixated,* s, *with the appearance of a left-beating (1°) nystagmus. After eye closure the eyes drift towards and through primary gaze. Superimposed on the drift is a right-beating nystagmus, of which the slow phase is to the left. Eventually the eyes are positioned in the right side of the orbit. When the eyes are opened, inappropriate movements are made until the eyes refixate the target and a left beating nystagmus is again seen.*

EOG drift negligible.

primary gaze. The movement is 'triggered' either by closing the eyes or darkness and takes the approximate shape of an exponential decay rather than a saccade. The whole movement lasts between 2 and 6 seconds. Eleven of the patients were unable to maintain eccentric gaze on eye closure (Figs. 2 and 3), though all maintained eccentric gaze with fixation. Gaze failure was present in darkness in 2 patients, both of whom had multiple sclerosis. With eye closure the patients failed to maintain gaze to both sides except in one case with a left-sided cerebellar tumour and brain stem involvement, in which the failure was only to the left. When the eyes returned towards centre the new neutral or null position of the eyes was not necessarily the primary position. This is illustrated in Fig. 3A, where the eyes tended to come to rest some 10° to the right of the primary position whether the initial gaze was to the left or right. The movement of the eyes follows an approximately exponential time course with a time constant of 0·5 to 1·5 seconds. Encouragement to maintain an eccentric position of gaze during eye closure resulted in feeble and unsuccessful corrective movements.

DRIFT MOVEMENT

The term 'drift movements' means wandering movements of the eyes, attaining velocities of only 1 or 2° per second and enduring for many tens of seconds. Removal of fixation by eye closure, darkness, or both resulted in slow drifting movements of the eyes in 9 of the patients. An example occurring in darkness is shown in Fig. 1B, where the eyes move nearly 40° to the right of the primary position, then drift slowly back past the midline. In other cases the drift appeared to be unidirectional, as in Fig. 2A and B, where there is a slow drift to the right of the midline. In the 5 cases in which there was evidence of a predominantly unilateral lesion the drift tended to be away from that side. Furthermore, in those cases where there was a failure to maintain eccentric gaze and the neutral position was displaced to one side of the position of primary gaze, the drift was also predominantly to the same side of the midline as this

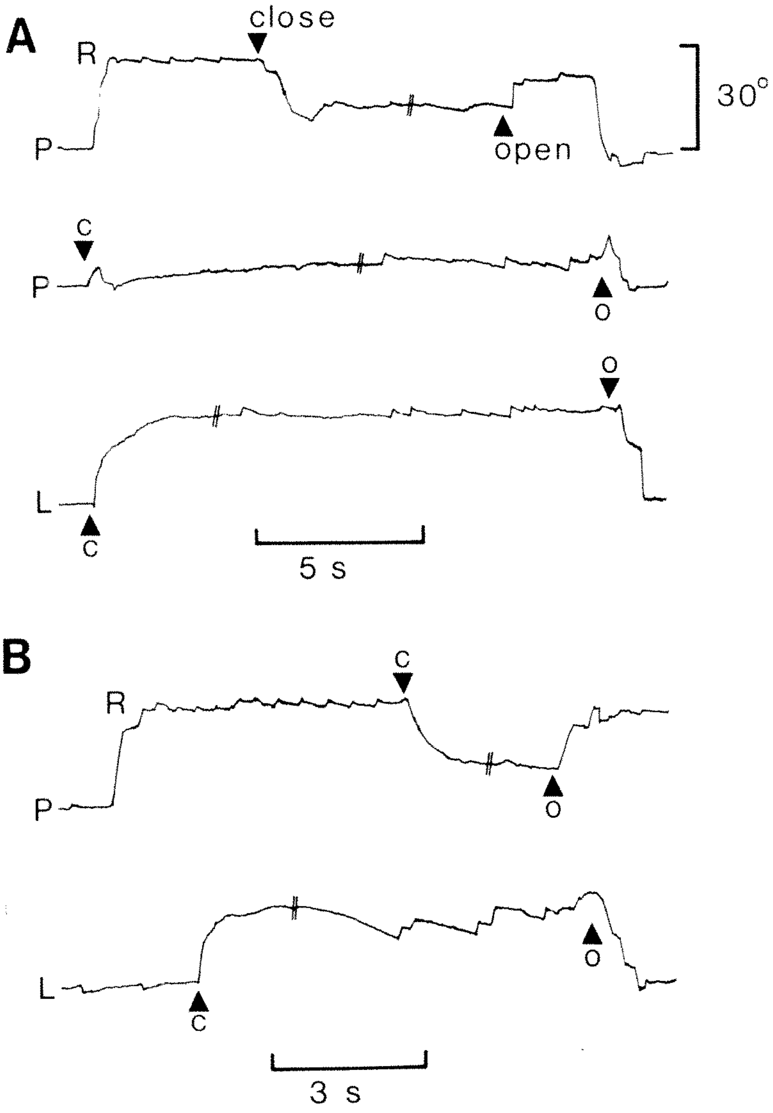

Fig. 3 A. *EOG recordings from a patient* (case 3) *with multiple sclerosis. When the eyes fixate a target 30° to the right a 1° nystagmus appears. Eye closure produces a rapid drift towards centre and abolishes the nystagmus. With eye closure* (C) *on primary gaze* (P) *there is a movement to the right with the appearance of a right-beating nystagmus. Eye closure* (C) *on left gaze* (L) *produces a rapid movement to centre with the appearance of a right-beating nystagmus.*

B. *EOG recordings from a patient* (case 4) *with a progressive cerebellar syndrome, probably due to multiple sclerosis. A right-beating nystagmus is evident on primary* (P) *and right* (R) *gaze; on left* (L) *gaze there is a left-beating nystagmus. On eye closure* (C) *there is a rapid movement of the eyes to the centre. On left* (L) *gaze a right-beating nystagmus develops with eye closure* (C).

EOG drift negligible.

O = *eyes open.*

new neutral position. When nystagmus was present during drifting eye movements, either the fast or slow phase could be in the direction of the drift (compare Fig. 2B with Fig. 1B). Of the 9 patients with drifting movements of the eyes all had gaze nystagmus and 8 had additional failure of gaze maintenance. Four patients had bilateral drift, the remainder had unilateral drift.

OTHER EYE MOVEMENT DISORDERS

Of the patients surveyed 14 had centrifugal nystagmus on lateral gaze, 10 had deranged pursuit movements, 7 had exaggerated caloric responses, and 6 had rebound nystagmus.

COMPARISON WITH THE CENTRIPETAL NYSTAGMUS AND EYE MOVEMENT DRIFT RESULTING FROM UNILATERAL LOSS OF LABYRINTHINE FUNCTION

Centripetally beating nystagmus is most commonly encountered in patients with loss of labyrinthine function when gaze is directed towards the side of the lesion. A typical nystagmus resulting from loss of end-organ function is illustrated in Fig. 4. The nystagmus is of a large-amplitude, saw-tooth type. The fast phase of the nystagmus carries the eyes towards the side of the intact labyrinth. In the presence of vision the nystagmus may be partly suppressed. In the absence of visual control of eye

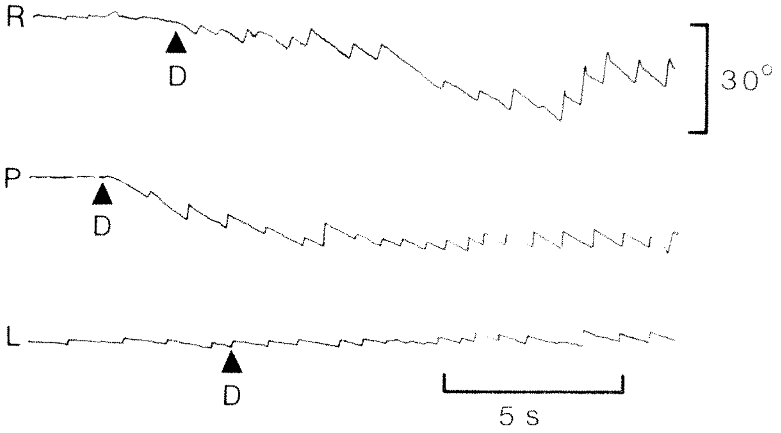

Fig. 4 *EOG recordings of eye movements in the horizontal plane in a patient with total loss of function of the left vestibular end organ.* R, L, *and* P *indicate that eyes are fixated on a target 30° to the right, left, or in primary gaze, respectively. At* D *the patient is in total darkness. EOG drift negligible.*

position there is an overall drift of the eyes in the direction of the slow phase. The velocity of the drift, as of the slow phase of the nystagmus, is inversely proportional to the magnitude of the displacement of the eyes away from the side of the intact labyrinth. When the gaze is towards the side of the absent labyrinth, the nystagmus beats centripetally.

Drifting eye movements and centripetal nystagmus in peripheral lesions may be distinguished from the similar eye movement signs which we have described in association with cerebellar disease in the following respects: (1) A peripheral nystagmus at any one time is unidirectional for all positions of gaze. In the absence of optic fixation a centripetal nystagmus in cerebellar disease may replace a centrifugal fixation nystagmus present in the same direction of gaze. (2) Drift in peripheral lesions is unidirectional. In cerebellar disease the drift may consist of alternate wanderings in either direction, although it may be unidirectional. (3) The slow phase of centripetal nystagmus in cerebellar disease may be in the opposite direction to that of the overall eye movement drift. In peripheral lesions drift and slow-phase movements are in the same direction.

In cases of unilateral loss of labyrinthine function partial recovery of end-organ function occurs after some time, and the peripheral nystagmus may reverse so that the fast phases are executed in the direction of the deranged labyrinth (Stenger, 1959). Although this is rare, when it does occur EOG records can be confusing, so alternative methods, such as caloric irrigation, must be used to establish the state of the vestibular end organs before a nystagmographic interpretation can be given.

Discussion

Westheimer and Blair (1974) have described the abnormalities of eye movement following cerebellectomy in the monkey, and these are particularly relevant to an understanding of our clinical findings. Immediately after hemicerebellectomy in mature animals the eyes fail to maintain lateral gaze (ipsilateral to the lesion) and drift centripetally. About a week later a compensatory bias towards the side of the lesion develops to counteract the gaze failure. The bias is present in all positions of gaze and is manifest as a drifting eye movement. If the eyes drift, visual (in the presence of fixation) and brain stem mechanisms which monitor eye movement sense the drift, and they correct for it by generating saccades, the net result being nystagmus. Hence the hemicerebellectomised adult monkey has a bilateral gaze nystagmus, due to gaze paresis ipsilaterally and to compensatory bias contralaterally. Any imbalance in the net sum of pathological and compensatory drift may result in an offsetting of the neutral resting position of the eyes. This shift of the 'rest point' of Holmes (1917), who observed it in lesions of the cerebellum, or the wandering 'neutral point' of Robinson (1974), who found it in cerebellectomised cats, is evident in some of our patients.

GAZE FAILURE

Fourteen of our patients had gaze nystagmus, of whom 13 had bilateral gaze failure in darkness or on eye closure. It is well known that eye closure produces a wide range of effects in the central nervous system. In our patients eye closure appears to shut down the brain stem mechanisms which normally monitor gaze position and correct it by generating fast phases of nystagmus and compensatory biases. The result is a failure of gaze maintenance, which when total implies additional brain stem lesions.

DRIFTING MOVEMENTS OF THE EYES IN DARKNESS OR UPON EYE CLOSURE

There are several possible sources of eye movement drift. In normal subjects a small centripetal drift is found with extreme lateral gaze in darkness (Becker and Klein, 1973). It is the presumed role of the cerebellum to generate a centrifugal compensatory bias to counteract this centripetal drift. The interplay between centripetal and centrifugal drift is shown by the fact that rebound nystagmus can be demonstrated in normals after prolonged eccentric fixation (Zee *et al.*, 1976).

In acute cerebellar lesions the balance between both centripetal and centrifugal drift is deranged. The centripetal drift is strong, even during fixation, resulting in ipsilateral fixation nystagmus (Holmes, 1917). It can be assumed that the counterbalancing centrifugal drift is lost immediately after the cerebellar lesion. In subacute and chronic cerebellar lesions, however, a compensating centrifugal drift can reappear. Robinson (1974) has shown that in the cerebellectomised cat the eyes wander in darkness. This has been interpreted as a failure to detect and nullify the low frequency noise of the oculomotor system with a consequent wandering of the neutral position point.

The drifting eye movements observed in patients with cerebellar disease closely resemble those found in animals following experimental lesions of the cerebellum, so it is likely that they can be attributed to the same mechanisms. Drift in a patient with a cerebellar lesion represents the algebraic summation of drift movements due to natural centripetal drift from eccentric gaze, loss of bias produced by the cerebellum to compensate for natural drift, drift caused by the development of new compensatory biases, and wandering of the neutral point due to low-frequency noise.

CENTRIPETAL NYSTAGMUS

When the eyes drift, a nystagmus is likely to occur, and centripetally beating nystagmus is generated when the direction of drift is away from primary gaze. As indicated above, eye movement drift is the result of summing pathological and compensatory biases. When this sum directs the eyes centrifugally, they drift outwards, producing the centripetal nystagmus. The lack of centrifugal drift in normal subjects, and the fact that it takes time to develop after a cerebellar lesion, suggest that when it occurs it is a sign of compensation. In cases of over-compensation centrifugal drift produces centripetal nystagmus. In matching compensation it induces the decay of gaze paretic nystagmus and the appearance of rebound nystagmus (Hood *et al.*, 1973; Baloh *et al.*, 1975; Zee *et al.*, 1976). The explanations offered for the phenomena of 'rebound' nystagmus (Hood *et al.*, 1973; Zee *et al.*, 1976) and 'periodic alternating nystagmus' (Daroff and Dell'Osso, 1974; Rudge and Leech, 1976) are similar to those involved to account for the drifting eye movements and associated nystagmus observed in the present study. The possibility exists that they are attributable to manifestations of the same basic mechanisms.

ORIGIN OF COMPENSATORY DRIFT

Visual mechanisms of fixation predominate and have the ability to rapidly 'switch off' centrally generated eye movement. This is clearly shown in Fig. 1B, in which the sudden appearance of a target returns the eyes to the lateral gaze and totally inhibits centripetal nystagmus. The situation is similar in 'recovery' nystagmus, in which rapid head shaking can immediately reverse its direction (Stenger, 1965). This is evidence that the mechanism responsible for producing compensatory 'biases' may be a common one.

Westheimer and Blair (1974) demonstrated the origin of the compensatory drift to be extracerebellar, the primary candidate being the vestibular nuclei. Indeed in many ways the phenomena seen after clinical and experimental cerebellar lesions are similar to the recovery phenomena observed after peripheral vestibular lesions (Stenger, 1959).

Recent neurophysiological evidence (Baker *et al.*, 1976; Baker *et al.*, 1977) would implicate the nucleus prepositus hypoglossi as an alternative candidate.

Conclusions

Certain eye movement signs have been systematically associated with cerebellar disease. These are (1) failure to maintain lateral gaze, (2) drifting eye movements in darkness or on closure, (3) offsetting of the neutral resting position of the eyes and gaze nystagmus which beats centripetally. Similar disorders of eye movements are seen in adult animals with experimental lesions of the cerebellum. All these disorders can be explained on the simple hypothesis that the cerebellum helps to maintain lateral gaze and that brain stem mechanisms monitor gaze position generating compensatory biases in the absence of normal cerebellar function.

APPENDIX

CASE 1 (see Fig. 1)

Vascular accident involving cerebellum and probably brain stem on left side

Three months before admission a 68-year-old man suddenly felt unsteady and giddy, and veered to the left on walking. Over the next few days he improved, but a week later he had a similar attack to the first and vomited profusely. He subsequently remained unsteady.

On admission to the National Hospital (Dr M. J. McArdle) the cranial nerves were found to be normal. Tone was normal in the upper limbs but slightly increased in the right leg. Power was normal. There was mild impairment of finger/nose/finger and heel/shin/knee testing on the left. Tendon reflexes were rather brisk, more in the right arm than the left, and were symmetrically brisk in the lower limbs. Plantars were flexor. The patient was unsteady and tended to veer to the left on walking. There was no sensory abnormality. Blood pressure was raised at 150/110 mmHg.

An air encephalogram and cerebrospinal fluid examination were normal. Formal neuro-otological examination revealed fine first-degree nystagmus to both sides, with rebound nystagmus. There was no positional nystagmus, and optokinetic responses were normal. There was a suggestion of a mild left canal paresis.

CASE 2 (see Fig. 2)
Left-sided cerebellar and fourth ventricular tumour removed 15 years prior to study
The patient presented at the age of 8 with headache, vomiting, and ataxia. He was admitted under the care of Professor Valentine Logue to Maida Vale Hospital. Examination at that time showed normal optic discs, a left sixth nerve palsy, some facial asymmetry—the right being lower than the left—first-degree nystagmus greater to the left than the right, and marked left-sided ataxia.

Ventriculography revealed symmetrical dilatation of the lateral ventricles, with displacement of the fourth ventricle to the right. At operation a low-grade cystic astrocytoma was found on the left side of the fourth ventricle, extending into the cerebellar hemisphere. Virtual total removal was achieved, apart from a small plaque of tissue on the floor of the fourth ventricle. After a course of radiotherapy all the symptoms resolved apart from a mild left-sided ataxia. Subsequently he developed episodes of unilateral headache associated with nausea, but did not consult his physician for the next 15 years, when his headaches became more troublesome, and he was referred back to the hospital. Examination revealed mild left-sided ataxia but no other convincing signs. EMI scan showed left cerebellar atrophy consistent with removal of the tumour and no evidence of recurrence. This was confirmed on lumbar air encephalography.

On formal neuro-otological testing he had mild left-sided perceptive deafness. Extraocular following movements were broken up, there was first-degree nystagmus to the left, and bilateral rebound nystagmus was present. There was a directional preponderance of the optokinetic nystagmus and caloric responses to the left.

CASE 3 (see Fig. 3)
Multiple sclerosis with evidence of cerebellar dysfunction
At 44, the patient developed paraesthesiae in both feet, which resolved over a period of 3 months. Approximately 6 months later the paraesthesiae recurred and then involved the left hand as well as the feet. At about the same time he noted some imbalance. These symptoms persisted for 1 year and he developed increasing unsteadiness of gait, with weakness of the legs over a period of 2 months. He was admitted to the National Hospital, Queen Square (Professor R. W. Gilliatt).

On examination at that time the cranial nerves were normal. In the upper limbs tone was increased on the left and there was a mild pyramidal weakness of that limb. There was bilateral finger/nose ataxis greater on the left than the right. In the lower limbs he had a spastic paraparesis, greater on the left, and moderate ataxia. His gait was markedly ataxic. Reflexes were brisk, plantar responses flexor, and the abdominal reflexes present. On sensory testing there was subjective superficial sensory impairment of the left hand and of the feet, with impairment of discrimination between two points in the left index finger.

Visual evoked potentials to a pattern stimulus were bilaterally delayed, indicating the presence of old optic neuritis. Formal neuro-otological examination showed directional preponderance of the optokinetic nystagmus to the left.

CASE 4 (see Fig. 3)
Progressive cerebellar ataxia, probably due to multiple sclerosis
A 30-year-old woman presented to the National Hospital, Queen Square (Dr Macdonald Critchley), with a 3½-year history of progressive deterioration of gait, difficulty in using the right hand, and slurred speech. There was no family history of neurological disorder.

Examination at that time showed marked cerebellar dysarthria. In the limbs tone was normal, but there was a mild weakness of finger and wrist extension, greater on the right, together with some weakness of hip flexion on the right. Co-ordination was moderately impaired in the upper limbs and grossly so in the lower. Reflexes were normal in the upper limbs and depressed or absent in the lower. Plantar responses were equivocal and the abdominal reflexes present. The gait was grossly ataxic, such that the patient was unable to stand without support. Sensation was intact.

Formal neuro-otological testing showed second-degree nystagmus to the right, first-degree to the left, and first-degree upwards. Following movements were broken up in the horizontal plane. There was a central type of positional nystagmus. Caloric responses were greatly enhanced but symmetrical. The optokinetic responses were grossly deranged in all directions, with almost complete suppression. Cerebrospinal fluid had a strongly paretic Lange curve, with negative serological testing for syphilis.

In spite of the progressive history it was concluded that the patient had multiple sclerosis in view of the spinal fluid findings.

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Anterior segment surgery early after corneal wound repair

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SUMMARY Penetrating wounds of the cornea require immediate repair, generally within 24 hours. Tight closure of the wound and a reformed anterior chamber are the primary goals of surgery. However, there is no guarantee that further surgery will not be required for maintaining the healthy function of the anterior segment. At the second operation the effect of the procedure on the previously repaired wound is of prime importance, since in many cases the operation needs to be done before corneal healing is completed. In our series the lens, which was either partially or completely cataractous at the initial operation, became intumescent at different times afterwards, and an immediate removal was necessary. No change in the preoperative wound sealing or transparency of the cornea could be detected after lens surgery performed between 24 hours and 21 days from the initial corneal repair.

The surgical repair of perforating corneal lacerations should be performed as early as possible. The steps are orientated towards a watertight closure of the wound, a reformed anterior chamber, and a free passage between posterior and anterior chamber. If these conditions are fulfilled in the first operation, visual function of the repaired globe is likely to be recovered to an important degree (Roper-Hall, 1959; Muga, 1975). However, in the early postoperative period complications such as phacomorphic glaucoma, hypertensive hyphaema, or extensive synechiae to the wound may occur. Few reports have been published on the management of these complications (Duke-Elder, 1972). A second operation may be required in many cases, with an uncertain effect on the freshly repaired wound.

In the present series the lens, which was partially or completely cataractous owing to the trauma, became intumescent after the initial repair of the perforating injury of the eye. The effect of an early surgical operation, to remove the traumatic cataract, on the previously repaired corneal wound and anterior segment is reported.

Materials and methods

The patients included in this series were originally operated on for repair of a perforating laceration of the cornea. The lens, either partially or completely cataractous at the time of the first operation, was left in place. At different times after the initial repair an intumescent cataract developed, causing a flat anterior chamber, angle-closure glaucoma, or lens-endothelial contact. These situations, when present, encouraged us to re-examine the case for removing the lens.

The first operation on these patients was performed by several ophthalmic surgeons. The indication for the second operation was decided, and the procedure itself carried out, by the authors. One hundred and thirty-five patients with a perforating injury of the cornea were admitted between June 1975 and June 1976 at the Dr Alejandro del Río General Emergency Hospital of Metropolitan Santiago. Of these, 14 cases presented an intumescent lens at different times after surgery (see Table).

The patients were subjected to the following procedure. Under general anaesthesia the eye was immobilised with a superior rectus stay suture. Through two limbal keratotomies, under a fornix-based conjunctival flap, at the 10 and 2 o'clock positions, the lens was aspirated and irrigated with two 20-gauge cannulas. Anterior lens capsule remnants were removed with the help of Von Mandach forceps and Vannas scissors. The iris was prolapsed and a peripheral iridectomy performed at the site of one of the keratotomies. The anterior chamber was reformed with air, and the keratotomies were closed

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Table *Early reoperation of perforating injuries*

Case	*Age (years)*	*Interval injury to 1st operation (hours)*	*Interval 1st to 2nd operation (days)*	*Cause of reoperation**	*Result of reoperation*		*Vision at 6 months*
					Dehiscence of repaired corneal wound	*Anterior chamber*	
1	14	24	21	*a, b, c*	none	deep	1·0
2	5	4	2	*a*	none	deep	0·2
3	7	3	1	*a, b*	none	deep	0·1
4	12	16	8	*a, b, e*	none	deep	0·3
5	24	144	4	*a, b, d*	synechiae to wound	flat	HM
6	6	2	1	*a, b*	none	deep	—
7	22	7	28	*a, b, e*	none	deep	0·5
8	60	4	4	*f*	none	deep	0·2
9	50	17	7	*a, c*	none	deep	NLP
10	6	30	8	*a, d*	none	deep	0·1
11	8	4	1	*a, b, c*	none	deep	0·8
12	15	5	1	*a, b*	none	deep	0·9
13	8	24	1	*a, d*	none	deep	0·3
14	12	4	3	*a, b, c*	none	deep	0·5

* *a*, intumescent cataract; *b*, flat anterior chamber; *c*, phacomorphic glaucoma; *d*, synechiae; *e*, lens-endothelial contact; *f*, cataract luxation

with an 8·0 Virgin silk suture. The first and second operations were done with a Zeiss operating microscope. In the postoperative period the patients were examined daily with a Haag-Streit slit lamp and observed for wound sealing, synechiae to the wound, corneal haze, anterior chamber depth, aqueous flare, infection, and glaucoma. The follow-up period ranged from 4 months to 1 year.

Results

Fourteen patients presented the features described above. In the Table the early postoperative period of the second operation is described as well as the cause that precipitated the reoperation. With the operation to remove the lens, sealing of the repaired corneal wound was affected only in Case 5, who presented a synechia of the iris to the wound and a flat anterior chamber. The remaining 13 cases had an unremarkable postoperative period.

Discussion

The healing process in perforating corneal wounds involves epithelial cells and fibroblasts in the anterior portion and endothelial cells in the posterior portion. Only after 7 months of healing does the scar, either in the anterior or the posterior portion, resemble undisturbed tissue (Matsuda and Smelser, 1973). This explains why the tensile strength of a repaired corneal wound in the first week after surgery is only 6% that of undisturbed cornea. By 3 weeks it is about 30% and 6 months later only 50% of that of normal tissue (Gasset and Dohlman, 1968). These basic aspects of corneal wound healing, in addition to the current clinical experience regarding fragility of a sutured corneal wound during the 4 weeks that follow cataract or graft surgery, make one reluctant to reoperate in a case with a freshly repaired corneal wound in a severely injured eye. However, the condition of the patients presented here gave no alternative to reoperation as the proper treatment to improve visual function expectations for the injured eye. Early reoperation for lens removal did not alter the preoperative state of the repaired cornea. Some authors consider that the lens damage coexisting with perforating injuries should be treated later as a separate problem when the eye has recovered from the initial injury (Duke Elder, 1972; Reinecke and Beyer, 1966). However, there are no reports of the frequency with which the lens acts as a focus of potential damage to the eye in the early postoperative period, i.e., phacomorphic glaucoma, flattening of the anterior chamber, or lens-endothelial contact. The prime concern is how the repaired wound will be affected with a second operation. The results in our present series indicate that aspiration–irrigation of the lens can be performed without altering the preoperative state of the cornea from the first day after the initial repair.

The authors are grateful to Elena María Korzenszky for secretarial assistance.

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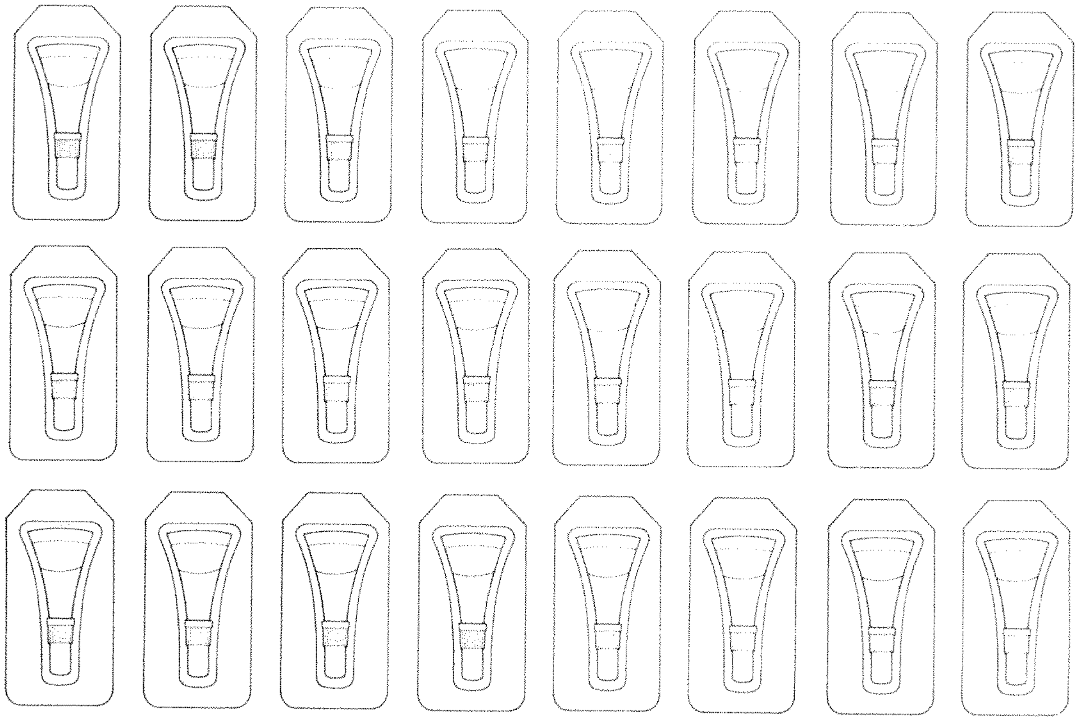

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Endothelial cell loss and corneal thickness after intracapsular extraction and iris clip lens implantation: a randomised controlled trial (interim report)

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SUMMARY Patients in a randomised controlled trial were chosen either to have iris clip lens implantation after intracapsular cataract extraction or intracapsular extraction only. They were assessed in terms of corneal thickness, postoperative epithelial oedema, and endothelial cell counts. All patients had 1 eye submitted to operation, which was carried out by the same surgeon. There was significantly greater increase in corneal thickness ($P<0.05$) on the 5th postoperative day in eyes which had lens implants (23 patients with intracapsular extraction and 19 with implant), but the difference between the 2 groups became insignificant at 1 month (17 patients in each group).

Daily corneal thickness measurements and observations of epithelial oedema in a subgroup (20 patients divided equally into 2 groups) showed that postoperatively there was greater and more widespread corneal oedema after implant surgery. When the operated eye was compared with the unoperated eye, endothelial cell loss was significantly greater in those with implants ($P<0.01$) than in those with simple intracapsular extraction.

Intraocular lens implantation after cataract extraction has regained general acceptance and is now widely practised. The reported incidence of various complications differs considerably, but the incidence of intractable corneal oedema would seem to be greater than expected from simple cataract extraction. This is also a complication which may be related to the trauma of additional steps entailed in implant surgery. Binkhorst and Leonard (1967) reported initial results in 124 eyes, treated over a period of 7 years and did not observe a single case of intractable corneal oedema. Jardine and Sandforth-Smith (1974) had reported an incidence of 10% in 70 cases. Pearce (1972, 1975), Jaffe and Duffner (1976), and Duffner *et al.* (1976) have reported an incidence of between 1·5 and 3·6% of serious corneal oedema. Pearce (1975) also reported an incidence of 13·2% of minor oedema which had not interfered with vision in the eyes studied.

When endothelial function is impaired, the corneal stroma may swell, with a resultant increase in thickness which may have no effect on vision until it exceeds 30%. Miller and Dohlman (1970) have reported a permanent increase in corneal thickness in patients after simple intracapsular cataract extraction. Giardini and Cambiaggi (1956) have reported prolonged thickening of the cornea after similar types of surgery. Wood and Maumenee (1975), studying patients operated on by more modern techniques, did not support the findings of Miller and Dohlman, which suggests that modern techniques perhaps cause less trauma to the endothelium. Cheng *et al.* (1977) have compared corneal thickness of eyes after lens implantation and after intracapsular extraction in a retrospective study, and no significant difference was found in corneal thickness between these two groups.

The purpose of this study was to compare two groups of patients in whom 1 eye was submitted to surgery and was randomly chosen to have either simple intracapsular extraction or iris clip lens implant after intracapsular extraction. Three measures were chosen for assessment: (1) Central corneal thickness, (2) epithelial oedema in the immediate postoperative period, (3) endothelial cell counts.

PATIENTS

All patients had uncomplicated senile cataracts. They were randomly allocated to one or other type of surgery. The age of the patients ranged from 55 to 84.

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EXCLUSION CRITERIA

Patients were excluded if they had corneal dystrophy or marked guttata, a previous history of iritis, a retinal hole or previous detachment, glaucoma, juvenile onset diabetes, myopia > 7 dioptres, or a shallow anterior chamber.

Methods

Microsurgical techniques were used for all operations, which were carried out by one of the authors (H.C.). At the time of the evaluation of this study his experience consisted of having carried out over 100 operations of iris clip lens implant following cataract extraction as a primary procedure. Eighty-six of the first 100 patients had been followed up for 6 months to 3 years, and their visual results are presented in Fig. 1.

TYPE OF IMPLANT

The Federov implant (Rayners and Keelers Ltd), with a cruciate arrangement of loops, or a modified iridocapsular lens of Binkhorst type was used (Fig. 2). The latter has an anterior peg made of Supramid, which can be fastened to the supero-posterior loop through the peripheral iridectomy and was a modification by one of us (H.C.).

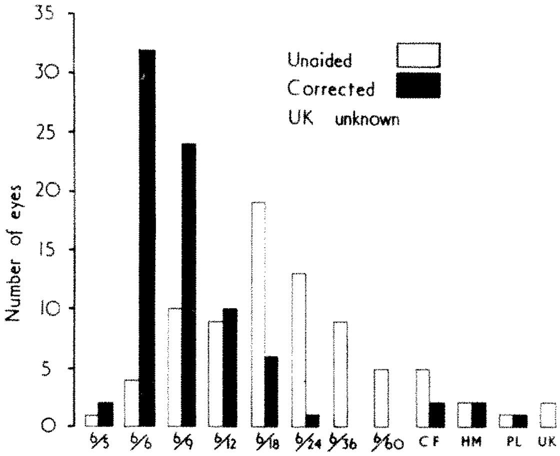

Fig. 1 *86 Patients (86 eyes) with follow-up of 6 months to 3 years (2 patients lost to follow-up)*

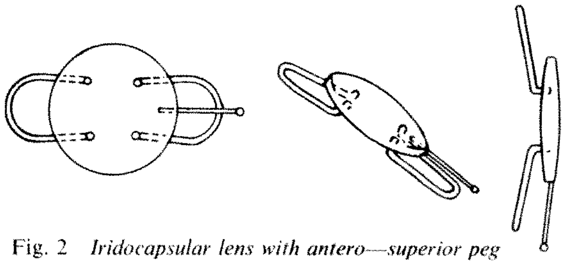

Fig. 2 *Iridocapsular lens with antero—superior peg*

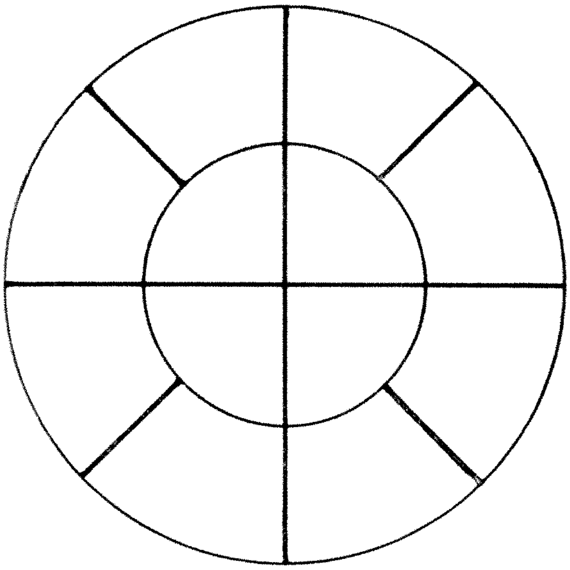

Fig. 3 *Schematic division of cornea into 12 sections*

TECHNIQUE

Corneal thickness. The Haag-Streit 900 Pachometer was used for all measurements. The Mishima modification was not used, but patients who could not fix steadily on a point source of light were excluded. A minor modification used in a previous study (Cheng *et al.*, 1977) was used, and the procedure was the same to ensure that the axial corneal thickness was measured. Both eyes of all patients were measured preoperatively and likewise at 5 days and 1 month postoperatively; 23 patients with intracapsular extraction and 19 with implants had measurements on the fifth day, and there were 17 patients in each group at 1 month. Twenty patients in the series had daily measurements from the preoperative day to the day when the corneal thickness of the operated eye became the same as the unoperated eye or when the patient had to be discharged because there was no reason to warrant his further stay in hospital. Ten of these patients had an implant in 1 eye, and the other 10 had simple intracapsular extraction in 1 eye.

EPITHELIAL OEDEMA

The cornea was divided into 12 sectors (Fig. 3). The number of sectors covered by epithelial oedema was recorded daily. Oedema confined to the wound edge was not included.

ENDOTHELIAL CELL COUNT

The same 20 patients with daily measurements had endothelial cell photographs. The specular microscope, with a camera attachment, was devised by Sturrock and Sherrard and was based on a principle of Maurice (1968). Ten photographs were taken of the endothelium of each eye at each photographic session; the mean cell count was measured. In 11 of the 20 patients there were pre- and postoperative photographs, but postoperative photographs only were obtained in 9 patients. Where there were preoperative photographs the percentage cell loss was taken to be the difference between the pre- and postoperative counts of the same eye. Where there were postoperative photographs only, the cell loss was taken to be the difference between the operated and unoperated eyes. The method of counting is described by Sturrock and Sherrard (in press).

IMPLANT-ENDOTHELIUM CONTACT

At the time of surgery the amount of contact was graded as 'considerable', 'moderate', or 'slight'. 'Considerable' was defined as a situation where the implant slid against the cornea during insertion or intracameral manipulation; 'moderate' where the cornea rested on the implant for more than 30 seconds or where there were up and down movements of the cornea against the implant; and 'slight' where the implant briefly touched the endothelium.

Results

CORNEAL THICKNESS

Table 1 includes the number of patients who had measurements on the fifth postoperative day and at 1 month. The mean increase in corneal thickness at 5 days was greater in eyes with implants than in those which had only a simple intracapsular extraction. The difference was statistically significant ($P < 0{\cdot}05$). At 1 month the mean increase in corneal thickness was not significantly different when the 2 groups were compared.

Table 1 *Increase in corneal thickness in the operated eyes*

Time of measurement	*Intracapsular extraction*		*Implants*	
	Mean increase (mm)	*Variance*	*Mean increase (mm)*	*Variance*
5th day postop.	0·0417	0·0018	0·0750	0·0032
	$n = 23$		$n = 19$	
		P < 0·05		
1 month postop.	0·0219	0·0005	0·0145	0·0007
	$n = 17$		$n = 17$	
		Not significant		

n = number of eyes

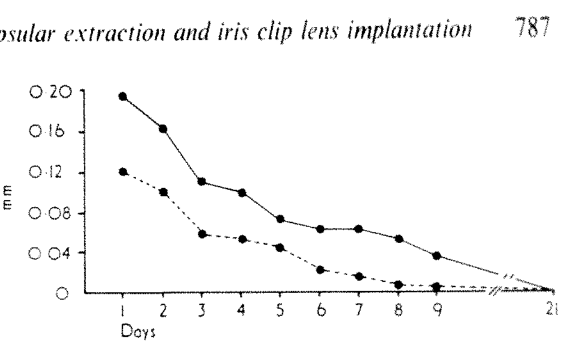

Fig. 4 *Mean difference in corneal thickness between operated and unoperated eyes. Day 1 = 1st postoperative day. ——— Implants. ------ Intracapsular extraction only*

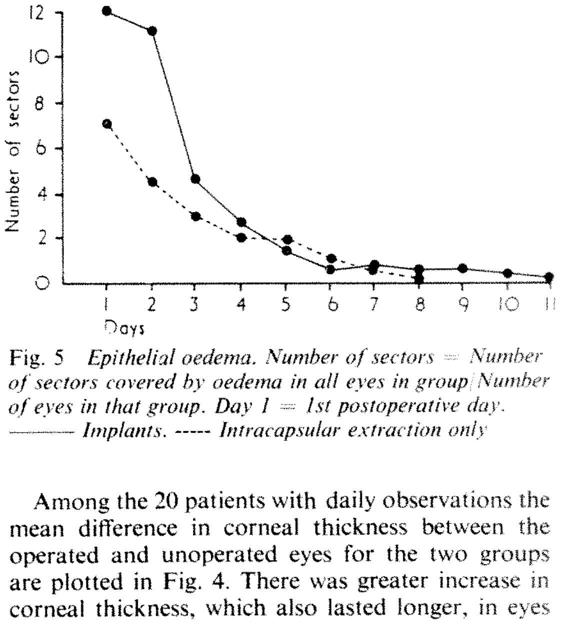

Fig. 5 *Epithelial oedema. Number of sectors = Number of sectors covered by oedema in all eyes in group/Number of eyes in that group. Day 1 = 1st postoperative day. ——— Implants. ----- Intracapsular extraction only*

Among the 20 patients with daily observations the mean difference in corneal thickness between the operated and unoperated eyes for the two groups are plotted in Fig. 4. There was greater increase in corneal thickness, which also lasted longer, in eyes with implants. The thickness values returned to normal for all operated eyes by 3 weeks.

EPITHELIAL OEDEMA

In the same 20 patients all implanted eyes had overall epithelial oedema on the first postoperative day compared to only 3 eyes after simple intracapsular extraction. Fig. 5 shows the mean number of sectors covered by epithelial oedema. There was a significant increase in the number of sectors involved in eyes with implants in the first 2 days ($P < 0{\cdot}01$), but there was no significant difference by the third postoperative day. Two eyes in each group had raised intraocular pressure on the first day, but all eyes were normotensive by the second day.

ENDOTHELIAL CELL COUNT

There were photographs of 31 unoperated eyes (22 eyes of 11 patients with preoperative photographs plus 9 eyes of the other patients with postoperative photographs only). The cell counts ranged from 1591 to 3579/mm. The difference in cell counts between the 2 eyes preoperatively and between the same unoperated eye pre- and postoperatively did not exceed 11% in any patient. The mean difference was 2·7%.

The cell loss for individual patients is listed in Table 2 for eyes with implants, and in Table 3 for those after intracapsular extraction. A number of patients developed complications which were listed against the initials of the patients. No surgical intervention was required for any of the complications.

The mean cell loss for the overall group of patients in the implant series was 41·3%, and for the intracapsular extraction series 21·4% (Table 4). If those eyes which had complications were eliminated from the series the percentage loss was virtually unchanged for those with implants but dropped to 14·5% for those which had intracapsular extractions only.

Table 5 shows the mean difference in cell counts between the right and left eyes in the 2 groups postoperatively. The comparison between the implanted eyes and those which had simple cataract extraction was statistically significant (P<0·01).

The amount of contact between the implant and the endothelium is given in Table 2. It shows that the 3 eyes with only 'slight' contact had the least cell loss. There was no close agreement between 'considerable' and 'moderate' contact and cell loss.

Table 2 *Endothelial cell loss compared with increased corneal thickness and trauma at operation (implanted eyes)*

Case	*% cell loss (or gain)*	*% increase in thickness*	*Contact between implant and endothelium*			*Complications*
			Considerable	*Moderate*	*Slight*	
1	63·4	56		+		
2	62·0	46		+		Large tear of Descemet (from section)
3	53·6	33		+		
4	53·0	46	+			Pupil block glaucoma (relieved by pupil dlln.)
5	51·0	41		+		
6	40·7	22	+			
7	40·0	60	+			
8	29·0	40·5			+	
9	19·5	27			+	
10	+0·1	50			+	Late shallowing of ant. chamber

PERCENTAGE INCREASE IN CORNEAL THICKNESS

The peak increase in corneal thickness was compared

Table 3 *Endothelial cell loss compared with increase in corneal thickness (intracapsular extraction)*

Case	*% cell loss (or gain)*	*% increase in thickness*	*Complications*
11	12·7	30	
12	11·8	30	
13	15·7	15	
14	2·5	18	
15	+0·3	20	
16	66·8	51	Leucocytes on endothelium vitreous in wound
17	44·5	48	Hypopyon and late choroidal detachment
18	+0·5	10	Pupil block glaucoma (relieved by dlln.)
19	16	5	Loss of AC (3 to 8 hours)

Table 4 *Mean endothelial cell loss and mean peak increase in corneal thickness*

	Category	*% mean cell loss*	*Mean % peak increase in thickness*
Overall group	Implants (10 eyes)	41·3	42·1
	Intracapsular extraction (10 eyes)	21·4	27·8
No complications	Implants (7 eyes)	42·6	39·9
	Intracapsular extraction (6 eyes)	14·5	26·5

Table 5 *Endothelial cell count—difference between 2 eyes (all patients had surgery to 1 eye only)*

	Intracapsular extraction	*Implants*
No. of patients	10	10
Mean difference in cell count/mm²	381	928
P<0·01		

with the preoperative value and expressed as a percentage (100% = preoperative value). With one exception the greatest corneal thickness occurred on the first postoperative day. Tables 2 and 3 show the percentage increase in thickness for each patient, and Table 4 shows the mean percentage increase for the overall groups as well as for those without complications.

Discussion

Cheng *et al.* (1977) in a retrospective study did not find any significant difference between the corneal thickness of eyes which had simple uncomplicated intracapsular extractions and iris clip lens implants. The patients studied had follow-up periods from 6 months to 4 years. This suggested that up to that time no decompensation had occurred in these eyes. However, in the present prospective study on larger numbers of patients there was a significant increase in corneal thickness on the fifth postoperative day in those eyes which had lens implants, which suggests that there is a significantly greater amount of endothelial injury after this type of operation. This finding is supported by the daily measurements of corneal thickness and epithelial oedema in a subgroup of patients, showing that corneal oedema is greater and more widespread in eyes after implant surgery. These findings correlate well with the amount of endothelial cell loss, which is significantly greater after lens implantation. The apparently close correlation between percentage increase in corneal thickness and percentage cell loss would suggest that 'functional impairment' bears a relationship with cellular depletion. However, the numbers studied were small, and when individual eyes were considered the relationship was less close than the mean values suggested. This would be in accord with our knowledge of hydration of the cornea, which depends on many factors (Mishima, 1968). The percentage cell loss both for eyes with implants and for those with simple extractions are in accord with those reported by Bourne and Kaufman (1976a, b) and Forstot *et al.* (1977). Though our number was small, it is interesting to note that the 3 implanted eyes with the least cell loss were recorded at operation to have only 'slight' contact between the lens and the endothelium. This could be explained by the work of Kaufman and Katz (1976), who showed that endothelial cells may be ruptured on contact with the methyl methacrylate implant. However, other factors can clearly cause endothelial cell loss. In our cases which had only simple intracapsular extraction there were 3 cases with a large percentage cell loss. Of the 3, 1 had no obvious cause. One had apparently abnormal cells with adherent leucocytes in the endothelial photographs and could have been abnormally susceptible to injury; he also had a knuckle of vitreous embedded in the wound postoperatively, although there was no vitreous loss at operation. Therefore, he could have had, in addition, an event leading to vitreous extrusion. The third patient had a hypopyon iritis, and her cell loss could have been due to inflammation.

At present there is no knowledge of the minimum number of endothelial cells required for healthy function of the cornea. Furthermore, present methods enable cell counts to be made only of a small axial area and may not be entirely representative of the counts in the corneal periphery. It is important to note that even when there is a reported cell loss of 80% the cornea may stay perfectly transparent and there is no increase in corneal thickness (Laing *et al.*, 1976b). Thus, the mere number of cells can be only one of many factors in maintaining normal corneal function. The work of Bourne and Kaufman (1976a, b) and Laing *et al.* (1976a) as well as of Sturrock and Sherrard (in press) would suggest that there is a gradual drop-out with age as well as with intraocular inflammation (Sturrock, personal communication). Therefore, the more widespread endothelial injury and the greater cell depletion after lens implantation would imply a lowering of endothelial reserve. Since lens implantation is now more widely practised, it is important for surgeons doing this operation to bear in mind the possible harm that may be inflicted and to take the utmost care to protect the endothelium during surgery.

We thank Mrs J. Cotton for her voluntary secretarial help, Miss P. Clifton for data handling, and the Knoop Trust for financial help.

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Correspondence

Stray light in the Tübingen perimeter

TO THE EDITOR, *British Journal of Ophthalmology*

SIR, I was interested in the paper by Weale and Wheeler (1977). As it happens I have been under suspicion of possibly suffering from incipient glaucoma and in the course of its investigation have had repeated field examinations, mainly on the Tübingen perimeter. I became aware, in viewing the target, of glare emanating from the lamp below, which is intended to illuminate background of the bowl. This definitely affected the visibility of the target, more especially of course in the lower field. I found that placing my hand below my chin eliminated this effect and I believe an obturator has been designed to eliminate the defect in the particular instrument on which I was tested. The problem did not arise in the Goldmann perimeter, whose design is different.

Perhaps it would be desirable for all ophthalmologists to try out their equipment themselves and, therefore, possibly discover unexpected difficulties.

Yours faithfully,
W. O. G. TAYLOR

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Greenock PA15 1TS

Reference

Weale, R. A., and Wheeler, C. (1977). A note on stray light in the Tübingen perimeter. *British Journal of Ophthalmology*, **61**, 133–134.

Measuring pupil size

TO THE EDITOR, *British Journal of Ophthalmology*

SIR, It is well known that variation in pupil size will affect visual acuity. This phenomenon has been a problem for those conducting epidemiological surveys of visual acuity, especially when the testing has been conducted in areas of direct sunlight. The problem is further compounded by the difficulty of measuring pupil size in people with heavily pigmented irides, in particular in dark-skinned races.

I have found a simple technique to overcome these difficulties. With commercially available macrophotography equipment it is relatively easy to photograph the eyes of a test subject at the time of testing. With the equipment set to the same magnification a photograph of a rule calibrated in millimetres is also taken. By first projecting the slide of the rule to determine the magnification on to the particular screen one can accurately measure the pupil size in projected slides.

Using this technique in the brightest summer conditions in Central Australia I have found that the pupil diameter of Europeans with blue irides ranges from 2·0 to 2·5 mm and that for full-blood Australian Aborigines the range is 2·0 to 2·6 mm.

Yours faithfully,
HUGH R. TAYLOR

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Notes

European Ophthalmic Pathology Society

The European Ophthalmic Pathology Society held its 16th Annual Meeting in Munich, Germany, on 14–17 June. The meeting was scientifically and socially of an exceptionally high standard and was excellently organised by Professor O.-E. Lund and Mrs Lund. It began with a reception by the Bavarian Government in the Residenz (residential palace). The Bavarian Ministerpräsident was represented by the Bavarian State Minister for Education and Culture, Professor Dr Hans Maier, and Mrs Maier. The reception was combined with a visit to the Schatzkammer (treasure chamber). The scientific meeting was held in the Hotel Bayerischer Hof, and the official dinner took place at the Palais Montgelas of this hotel. The social programme furthermore comprised attendance at the opera *Tosca* at the National Theatre, and the last day of the meeting ended with a visit to the Schleissheim and Lustheim castles and a boat tour on the Lake Starnberg bringing the company to the restaurant Berg for an informal Bavarian dinner. Dr W. R. Green (Baltimore) was the honoured guest. The next meeting of the society will be held in Belgrade, Yugoslavia, with Professor Olga Litricin as organising secretary.

Glaucoma Course

The Glaucoma Service of the Wills Eye Hospital will hold its annual glaucoma course on 14–15 April 1978. The cost will be $175 ($50·00 for residents with accompanying letter from department chief), which includes course and meals. Further information from Kenneth Benjamin, MD, 1419 Spruce Street, Philadelphia, Pennsylvania 19102, USA.

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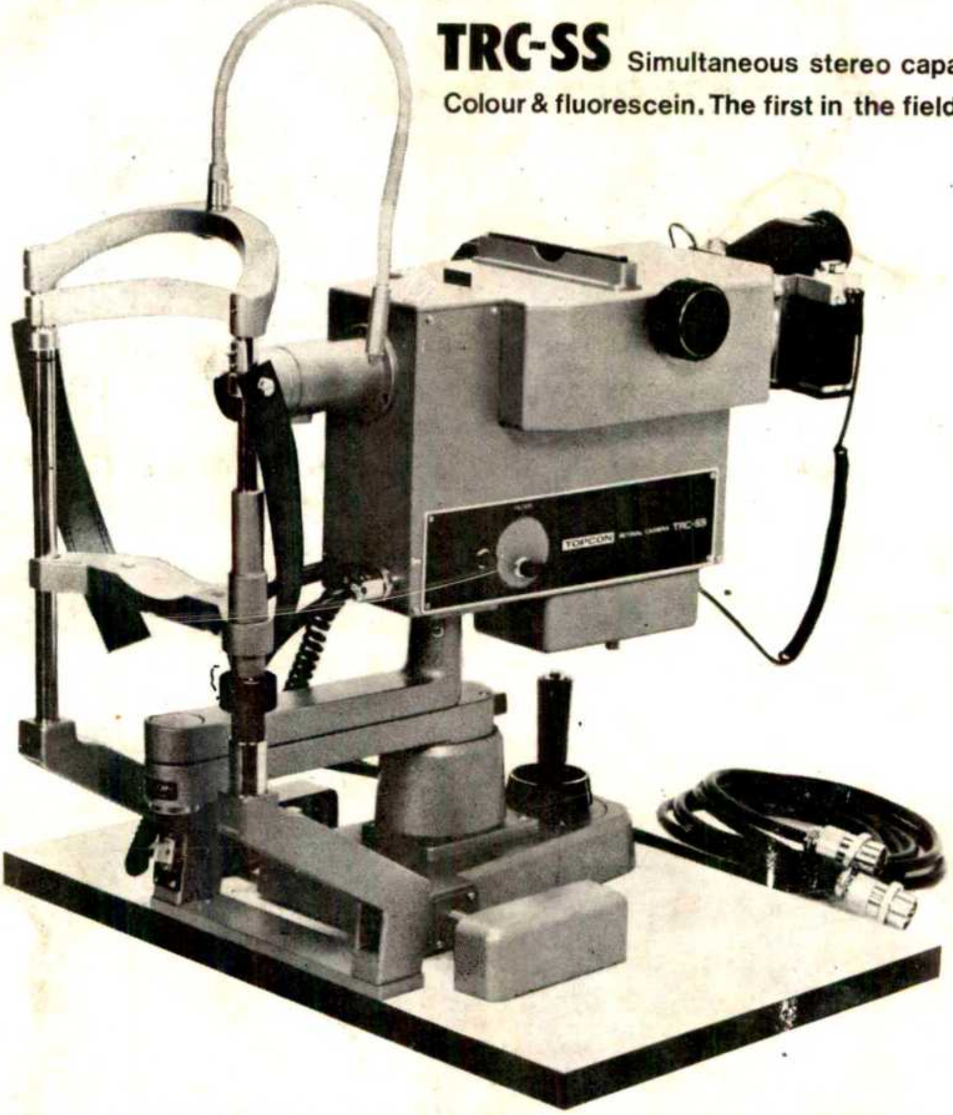

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